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**Using stated preferences to estimate the impact and
cost-effectiveness of new HIV prevention products in South Africa**

MATTHEW QUAIFE

**Thesis submitted in accordance with the requirements for the
degree of**

Doctor of Philosophy of the University of London

September 2017

Department of Global Health and Development

Faculty of Public Health and Policy

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

Funded by the Economic and Social Research Council

Research group affiliation(s): Health Economics and Systems Analysis
 Social and Mathematical Epidemiology

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Abstract

This thesis aims to deepen our understanding of the impact and cost-effectiveness of new HIV prevention products in South Africa. It explores how stated preferences for products vary across groups, and uses these data to estimate their cost-effectiveness in different populations. Also, it seeks to predict how products themselves may change the economics of sex work and lead to risk compensation among female sex workers (FSWs). The validity of predicting behaviours through the use of stated preference methods is explored through a systematic review and meta-analysis.

By integrating methods from the fields of health economics and infectious disease modelling, this thesis aims to give better predictions of the potential impact and cost-effectiveness of HIV prevention products. This is a paper-style thesis which incorporates seven papers and a short correspondence publication, linked by short pieces of supporting material.

The thesis finds that products offering effective multipurpose protection would be cost-effective among younger female groups and FSWs. However, it predicts that products could change the economics of sex work, potentially leading to risk compensation among FSWs. A dynamic transmission model is used to show how this risk compensation could meaningfully reduce product impact. This thesis demonstrates the value of combining economic and epidemiological modelling methods to explore preventative behaviours in HIV. Further work is needed to assess the external validity of these methods.

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First, I would like to thank my supervisors, Fern Terris-Prestholt and Peter Vickerman, for giving me the guidance and confidence to tread the hazy line between economics and infectious disease modelling. I feel very fortunate to have benefitted from your synergistic skills and working styles. The thoughtful comments of Mylene Lagarde, Marie-Claude Boily, Tara Beattie, and Aurelia Lepine have also greatly enhanced this work. The financial support of an Economic and Social Research Council 1+3 studentship was invaluable, as was project funding from the Bill and Melinda Gates Foundation and USAID via PATH.

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This thesis is dedicated to the memory of Daniel Hickey, for showing us that every avoidable death of a young person is a tragedy.

"You're original, cannot be replaced"

Perry, K et al. 2010. *Firework*. New York: Capitol Records.

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List of Abbreviations

AGYW	Adolescent girls and young women
AIC	Akaike information criterion
AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy/treatment
ARV	Antiretroviral
AUC	Area under the curve
BMGF	Bill and Melinda Gates Foundation
BWS	Best-worst scaling
CDC	US Centers for Disease Control and Prevention
CPC	Center for Positive Care, Ekurhuleni
CV	Contingent valuation
DALY	Disability-adjusted life year
DCE	Discrete choice experiment
FSW	Female sex worker
GBP	Great British Pound
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee, University of the Witwatersrand
ICER	Incremental cost-effectiveness ratio
IDU	Injecting drug users
IPV	Intimate partner violence
LC	Latent class
LSHTM	London School of Hygiene and Tropical Medicine
MMNL	Mixed multinomial logit
MNL	Multinomial logit
MPT	Multipurpose prevention technology
MSM	Men who have sex with men
NPV	Negative predictive value
NSP	South African National Strategic Plan for HIV/AIDS
PPA	Predicted probability analysis
PPV	Positive predictive value
PSA	Probabilistic sensitivity analysis
RDS	Respondent-driven sample
RP	Revealed preference
RUT	Random utility theory
SP	Stated preference
SROC	Summary receiver operating characteristic curve
STI	Sexually transmitted infection
USAID	United States Agency for International Development
USD	United States Dollar
VMMC	Voluntary medical male circumcision
WHO	World Health Organisation
Wits RHI	Wits Reproductive Health and HIV Institute
WTP	Willingness-to-pay
ZAR	South African Rand

Chapter 1: Introduction

Scope of thesis

This thesis presents work which deepens our understanding of the impact and cost-effectiveness of new antiretroviral (ARV)-based HIV prevention products in South Africa. It seeks to estimate how demand for different products will vary, and models the impact of this variation on the epidemic. Also, it explores how products themselves may change risk behaviours among female sex workers (FSWs). By integrating methods from the fields of health economics and infectious disease modelling, this thesis aims to give better predictions of the potential impact and cost-effectiveness of prevention products.

This thesis details the development and application of two discrete choice experiments (DCEs) which are used to estimate the impact of new antiretroviral (ARV)-based HIV prevention products in South Africa. The first hereafter referred to as the “products DCE”, seeks to predict the uptake of new multipurpose prevention technologies (MPTs) among four populations of potential users in South Africa. The second hereafter referred to as the “FSW DCE”, aims to predict risk compensation in the form of increased provision of unprotected sex, attributable to use of an effective prevention product by HIV negative FSWs. Results from both DCEs are presented as standalone results papers (indicated by “R”): R1 is used to parameterise product uptake and condom substitution in paper R2, and R3 to inform a broader microeconomic framework of FSW risk compensation in paper R4.

This is a paper-style thesis which, over 10 chapters with appendices, presents seven papers and one correspondence publication, linked by short pieces of supporting material and sections of additional information. This means that some material is repeated, particularly background information and citations in research papers. I have endeavoured to keep this to a minimum, for example by presenting methodological detail once in the results papers themselves. For this reason, the thesis does not use

typical Introduction-Methods-Results-Conclusions headings, though this is its broad structure. For consistency throughout, references are listed at the end of each chapter or research paper.

Outline of thesis

This introduction chapter (chapter 1) briefly describes how the human immunodeficiency virus (HIV) epidemic has developed in South Africa. It then outlines recent advances in treatment and prevention that offer promise in tackling the South African and other HIV epidemics. In particular, it details the development of antiretroviral (ARV)-based prevention products – implemented as pre-exposure prophylaxis (PrEP) – which are the focus of this thesis. The remainder of chapter 1 outlines the overall objectives of the thesis, and lists its aims organised by research paper, before detailing the intellectual ownership of the research in the thesis and the involvement of the candidate in each activity.

The background section in Chapter 2 begins with a summary of mathematical modelling of infectious diseases, before focusing on key applications to impact and cost-effectiveness work within HIV. The chapter then highlights gaps in the literature where economic methods – specifically different applications of discrete choice experiments (DCEs) – could be gainfully employed. The theoretical underpinnings of DCEs are then described, followed by some relevant examples of their use. chapter 3 presents a research paper, a systematic review of the literature exploring economic influences on the choices and behaviours of FSWs. The final section of this chapter summarises important gaps identified in the literature and describes how this thesis intends to contribute to them.

Chapter 4 presents a paper detailing a systematic review and meta-analysis of the predictive ability of DCEs, which is currently under revision. DCEs are used in this thesis

to predict health-related behaviours; this paper describes and synthesises published evidence on the validity of DCEs for this application.

Chapter 7 presents the protocol for the products DCE, published in 2016 in *BMJ Open*. This paper details the primary data collection process and gives information on the formative development of the products DCE. Chapter 8 reports on the formative research to develop the products DCE, and describes the development and testing process of the FSW DCE. Additional information on the design and implementation of fieldwork is provided in the protocol paper of appendix IX, a 2016 publication from *BMJ Open*.

Chapters 6 to 9 present four results papers. Chapter 6, paper R1, describes the results of a DCE eliciting preferences for potential MPT products. Chapter 7, paper R2, uses uptake predictions from paper R1 to parameterise a cost-effectiveness model for MPTs among different population groups in South Africa. Chapter 8, paper R3, describes the results of a second DCE, which estimates how the introduction of a fully effective HIV prevention product might affect condom use and pricing in commercial sex work. Chapter 9, paper R4, combines these results with microeconomic theory in a dynamic transmission impact model to assess how changes in the economics of commercial sex – specifically on the supply-side – might affect the total impact of new HIV prevention products.

Finally, Chapter 10 presents a discussion summarising and synthesising the key empirical and methodological contributions of the thesis. I reflect on the strengths and limitations of the approaches taken in the thesis, before discussing the implications of findings for further research and policy. The thesis ends with a brief conclusion. Figure 1 shows the thesis structure, and Table 1 outlines the submission stages of each paper.

Figure 1: Outline of thesis

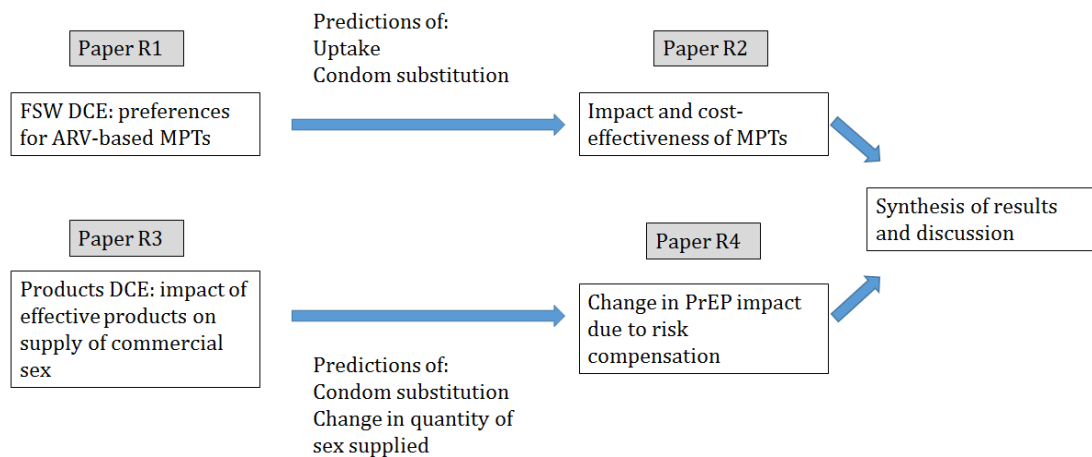


Table 1: Outline of Chapter submission and publication status

Chapter	Title	Submission status
1	Introduction, aims and objectives	Unpublished, for thesis only
2	Background on economic and modelling methods	Unpublished, for thesis only
3	Economic influences on female sex worker choices: A literature review	Not yet submitted
4	How well do discrete choice experiments predict health choices? A systematic review and meta-analysis of external validity	Accepted – European Journal of Health Economics
5	Additional information on the formative phase of DCE development	Unpublished, for thesis only
6	Paper R1: Divergent preferences for HIV prevention: A discrete choice experiment for multipurpose HIV prevention products in South Africa	Accepted – Medical Decision Making 2017
7	Paper R2: The cost-effectiveness of multipurpose HIV and pregnancy prevention technologies in South Africa	Accepted – Journal of the International AIDS Society
8	Paper R3: The effect of HIV prevention products on the supply of condomless commercial sex amongst female sex workers in South Africa	Revise and resubmit received – Health Economics
9	Paper R4: Modelling the epidemiological impact of changing incentives in sex work due to HIV pre-exposure prophylaxis	Not yet submitted
10	Discussion	Unpublished, for thesis only

The HIV epidemic in South Africa

South Africa has the world's largest and highest profile HIV epidemic. It is estimated that 7 million South Africans live with HIV, a prevalence of 19.2%[1]. Although 180,000 people died from HIV-related conditions in 2015[2], this is a marked reduction from the 320,000 deaths that occurred in 2010[2]. Progress in addressing the epidemic has been rapid since 2008, and South Africa now has the world's largest ARV treatment programme in the world: 4 million people received treatment in 2014, 47% of all people living with HIV in the country[3].

Notably, this HIV response has been largely funded from domestic resources, and the country invests more than \$1.5 billion annually to run its HIV and AIDS programmes[2]. This progress has led to a "turning tide" of HIV incidence, which has reduced among most age categories[4]. Also, a largely evidence-based policy response has resulted in policies which are comparatively progressive for the region, such as removing CD4 cell counts on treatment initiation, and making oral PrEP available to FSWs and other high-risk groups through public facilities[5, 6].

Epidemiological variation and structural influences on HIV risk

Today, the health and economic burden of HIV in South Africa is not borne equally[6]. Women are 40% more likely to be living with HIV than men, with a national prevalence of 14% compared to 10%. Adolescent girls (aged 15-19 years) face an 80% cumulative lifetime risk of HIV acquisition[4, 7]. In 2012, HIV incidence among women aged 15-24 was around four times greater than among men the same age; this age group accounted for 25% of new infections in South Africa[4]. Among women, HIV prevalence is highest among those aged 30-34 (36%), and slightly alter among men (29% at 35-39 years old). Differences in HIV prevalence by age between genders has been partly attributed to age disparate relationships (with an older male partner).[11-13]

In response to this disproportionate burden of risk, the South African National Strategic Plan on HIV, TB and STIs 2017-2022 (NSP) notes:

“Given the degree to which transmission among adolescent girls and young women is driving HIV across the country, every province, district and ward must take steps to intensify efforts to reduce new HIV infections and increase service access for adolescent girls and young women, including addressing the social and structural factors that increase vulnerability.”[3]

The NSP also speaks of “prioritising” the South African response to meet the needs of other key populations, including sex workers[3]. FSWs are around four times more likely to be living with HIV than other South African women of reproductive age[14]. They face an extremely high risk of HIV acquisition as they report a large number of sexual partners, can face barriers to negotiating condom use and are often unable to engage with health systems due to criminalisation and stigma[15, 16]. The extent to which FSWs engage with treatment and prevention services may have a substantial impact on transmission from FSWs to the general population[17].

Poverty, the relatively low status of women, and intimate partner violence (IPV) have been attributed as causes of the disparity in HIV prevalence between genders, with IPV attributable to around 20% of new HIV infections in young women[9, 10]. Vetten and Bhana [18] postulate four possible causal links between intimate partner violence and HIV risk: 1) violence leading to female genital injury, associated with increased transmission risk; 2) physical and non-physical abuse resulting in diminished negotiating power for condom use; 3) sexual abuse of a minor, which is associated with a greater likelihood of riskier sexual behaviour later in life; and 4) women who reveal a positive HIV status to a partner being subjected to abuse.

Finally, although contested as a theory [11, 12], age-disparate relationships between adolescent girls and young women (AGYW) and older men are also thought to contribute

substantively to the increased prevalence among young women compared to men of the same age[19].

Historical context

South Africa has not always been a leader in the HIV response. Between 1999 and 2008, Thabo Mbeki's presidency criticised evidence showing that HIV caused AIDS[20]. In 1999 Mbeki announced that the government would not provide the ARV zidovudine, used for the prevention of mother-to-child transmission (PMTCT), on unsubstantiated grounds that it was toxic and dangerous[21]. Later, Mbeki's government restricted the provision of the ARV nevirapine, although it was made available to South Africa free of charge by funders[22], and obstructed South African applications for global fund grants ([23], cited in [24]). Chigwedere et al. estimate that this restriction of ARVs between 2000 and 2005 caused the loss of 330,000 lives, and led to 25,000 babies acquiring HIV at birth[24].

The history of HIV/AIDS in South Africa cannot be separated from the socio-political upheaval of its transition from a racist white-minority government to a one-person one-vote democracy.

"The heart stopping euphoria of the 1994 elections, when South Africans cast their votes in a democratic, non-racial election for the first time, could not alter the profound economic, social and cultural dislocations of apartheid society, given their scale and historical entrenchment."[25] p.44

The scars of apartheid are still very apparent in today's South Africa, where affluent white suburbs sit alongside poor, mostly-formalised townships which almost exclusively house black South Africans. The neoliberal economic policies pursued first by the apartheid government of the 1980s, and then by the post-apartheid Mandela government in the late-1990s, have reinforced the migrant labour system that has supported the South African economy since the discovery of minerals in Kimberley and

the Rand in the late nineteenth century. In the late 1990s, Mark Lurie, then of the South African Medical Research Council described the situation:

“If you wanted to spread a sexually transmitted disease, you’d take thousands of young men away from their families, isolate them in single-sex hostels, and give them easy access to alcohol and commercial sex. Then, to spread the disease around the country, you’d send them home every once in a while to their wives and girlfriends. And that’s basically the system we have.”[26]

Despite facing enormous epidemiological, economic, and social challenges, South Africa’s recent HIV-related policies have led to a substantial increase in the proportion of HIV positive persons who know their status, are on treatment, and who have an undetectable viral load[3]. This has been associated with a reduction in HIV incidence and a decreasing AIDS-related death rate. The 2017-2022 NSP aims to make further progress in reducing HIV-related mortality and morbidity by achieving the UNAIDS 90-90-90 targets by 2020(ibid.).

HIV prevention

In recent years, clinical trials have shown that antiretroviral (ARV)-based pre-exposure prophylaxis (PrEP) can be efficacious in preventing the transmission of human immunodeficiency virus (HIV)[27-31]. However, protection has been variable across trials, and different PrEP delivery systems have conferred less protection to younger women[30, 32]. In particular, topical PrEP delivered through microbicide gels was thought to be a promising, female-initiated HIV prevention option, but performed poorly in clinical trials[33]. Both oral and topical PrEP products have been more effective in men-who-have-sex-with-men (MSM) populations than females[27, 34, 35], with this difference thought to be partly explained by adherence, and partly by pharmacokinetic data, showing higher colorectal drug concentrations compared to those in the female

lower genital tract[32, 36], i.e. providing higher protection against anal than vaginal transmission.

Trial data have shown that oral PrEP has high efficacy among many groups[27], and in May 2017 there were 55 ongoing or planned PrEP demonstration or implementation studies worldwide[37]. In South Africa, oral PrEP has been available to FSW and other high-risk groups since 2016, following the publication of national guidelines for implementation[5], and a number of projects are working to evaluate the impact of targeting oral PrEP distribution among AGYW groups[38].

A promising field of HIV prevention is the development of multipurpose technologies (MPTs), products which simultaneously provide protection from two or more of HIV, other STIs, and unintended pregnancy[39, 40]. Current MPTs in development include: 1) long-acting drug delivery systems such as intravaginal rings designed to protect from HIV infection and pregnancy (currently in a phase-I trial, ClinicalTrials.gov Identifier: NCT02235662); 2) pericoital drug delivery systems such as vaginal gel, tablets, and films designed to protect from HIV; and 3) a combination of products such as a contraceptive diaphragm used with microbicide gel designed to protect from HIV, STIs, and pregnancy[39, 41]. A short correspondence paper, provided as Appendix I, gives further details of the promise of MPTs in aiding the HIV response.

Aims and Objectives

The overall aim of this thesis is to assess the potential impact and cost-effectiveness of new HIV prevention products in South Africa by eliciting the stated preferences of men, women, adolescent girls, and FSWs. The objectives of this thesis are:

- 1) To quantify the determinants of demand for new HIV prevention technologies among adult men, women, and adolescent girls in the general population, and female sex workers

- 2) To estimate the impact and cost-effectiveness of new HIV prevention products among South African men, women, adolescent girls and female sex workers
- 3) To assess whether HIV prevention products will change female sex worker preferences for the supply of condomless commercial sex
- 4) To explore if changing incentives in sex work could substantially affect the impact of HIV prevention products through risk compensation
- 5) To identify key findings from this thesis and discuss the implications for the introduction of HIV prevention products

An additional methodological objective is:

- 6) To assess the reliability of discrete choice experiments to predict health-related choices

Four research papers make up the results section of this thesis, each answering one of these questions, while the fifth is tackled in the discussion. The research questions addressed in each paper are as follows:

Paper R1: *Divergent preferences for HIV prevention: A discrete choice experiment for multipurpose HIV prevention products in South Africa*

1. To explore which products are most attractive to potential users
2. To estimate the importance of other product characteristics, relative to HIV prevention
3. To identify key similarities and differences in preferences across populations

Paper R2: *The cost-effectiveness of multipurpose HIV and pregnancy prevention technologies in South Africa*

1. To use DCE data to predict uptake of candidate single- and multi-purpose HIV prevention products among female population groups in South Africa

2. To estimate the impact and costs associated with different scenarios of product introduction and rollout
3. To highlight where introducing products is likely to be most cost-effective

Paper R3: *The effect of HIV prevention products on the supply of condomless commercial sex amongst female sex workers in South Africa*

1. To explore the key factors driving client and act-type choice among FSWs
2. Assess how the use of an effective HIV prevention product will affect act price and levels of condom use
3. To explore heterogeneity in preferences for act and client characteristics

Paper R4: *How could risk compensation change the impact of new HIV prevention products? Modelling stated preference evidence from female sex workers*

1. To explore how a new HIV prevention product could affect the economic environment of sex work and lead to risk compensatory behaviours among FSWs
2. To estimate the effect of potential risk compensation on product impact by integrating epidemiological and economic modelling in a single methodological framework
3. To explore the sensitivity of model estimates to key behavioural parameters

An additional methodological paper is included in the methods Chapter. This paper assesses the suitability of using DCEs to predict health-related behaviours:

Paper: *How well do discrete choice experiments predict health choices? A systematic review and meta-analysis of external validity*

- 1) To systematically review and synthesise literature assessing the predictive ability of DCEs in health contexts
- 2) To critically appraise the potential for DCEs to inform predictions of future health-related behaviours

Intellectual Ownership

This research was undertaken as part of work supported by the Bill and Melinda Gates foundation, which covered fieldwork costs, and USAID, which covered data analysis alongside impact and cost-effectiveness analysis. The DCE exploring preferences for new HIV prevention products (Paper R1) was conceptualised by Fern Terris-Prestholt as an extension to previous research.[42] I led all stages of this DCE, from design to analysis, except the shortlisting of potential attributes for the DCE which was started before I joined the project.

I led all other elements of the research contained in this thesis, with support and advice from my supervisors, advisory committee and upgrading examiners. Although the cost-effectiveness paper (paper R2) was designed to meet project deliverables for USAID, the analysis plan, modelling methods, and paper writing were my work. A summary of my contribution to each of the research activities in this thesis is provided in Table 2.

Table 2: Summary of the role of candidate in research activities

Component	Activity	Responsibility	Additional input
Preparatory work	Development of project objectives and work plan	MQ, FTP	
	Site selection	MQ, FTP	WRHI, PRD
	Ethics submission and amendments	MQ, FTP, FC	
	Local authority permissions	MQ	WRHI, PRD
DCE development (both DCEs)		<i>Products DCE:</i> MQ, FTP, FC <i>FSW DCE:</i> MQ	
	Attribute shortlisting		WRHI
	DCE statistical designs	MQ	FTP
	Development of survey tools	MQ	FTP, WRHI
Data collection	Pre-piloting and pilot planning	MQ, PRD	FTP, WRHI
	Focus group guide development	MQ, WRHI	PRD
	Focus group conduct and survey data collection	PRD	MQ, WRHI
	Selection of survey sites	MQ, FTP, PRD	
	Training of interviewers	MQ, PRD	
	Analysis of pilot data, redesign of survey and DCEs	MQ	FTP
	Survey enumeration	PRD	MQ, WRHI
Research papers	Data analysis	MQ, FTP, PV	WRHI
	Paper R1: <i>Divergent preferences for HIV prevention: A discrete choice experiment for multipurpose HIV prevention products in South Africa</i>	MQ	FTP, PV, WRHI
	Paper R2: <i>The cost-effectiveness of multipurpose HIV and pregnancy prevention technologies in South Africa</i>	MQ	PV, FTP, WRHI
	Paper R3: <i>The effect of HIV prevention products on the supply of condomless commercial sex amongst female sex workers in South Africa</i>	MQ	FTP, PV, WRHI
	Paper R4: <i>How could risk compensation change the impact of new HIV prevention products? Modelling stated preference evidence from female sex workers</i>	MQ	PV, FTP, WRHI
Supervision	Overall project (BMGF/USAID Deliverables)	FTP, PV	WRHI
	Overall PhD/Thesis	FTP, PV	

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Chapter 2: Background on economic and modelling methods

This chapter presents background information on the economic and modelling methods used in this thesis. In particular, it seeks to identify gaps in these modelling methods and notes how they could be improved through integration with economic approaches.

First, I present an overview of why impact and cost-effectiveness modelling is useful in HIV prevention by summarising key methodological advantages alongside notable examples of its use in HIV prevention. Second, I give an overview of the background of, and rationale for, using DCEs to inform modelling work. Third, I summarise key gaps in the literature and their implications for this thesis.

Background and the role of modelling in HIV prevention

This section provides background information on the development and use of mathematical modelling in the HIV field.

Mathematical models of infectious disease

Infectious disease epidemics dominated public health in the nineteenth and twentieth centuries. However, advances in the treatment of disease and a greater understanding of pathogens and their transmission has seen morbidity and mortality from infectious disease reduce markedly[1]. A large number of infectious diseases are now curable or preventable in middle- and lower-income contexts, yet many – including HIV – are not, and still have a substantial and persistent impact on population health.[2] Mathematical models are used to describe and analyse the characteristics of infectious diseases to evaluate potential interventions to reduce ill health.[3, 4]

A mathematical model is “a representation of the essential aspects of an existing system[...] which presents knowledge of that system in usable form” (Ekyhoff (1974), cited in Young 1981[5]). Mathematical models of natural systems have been used for centuries in the natural and social sciences, and use sets of equations to describe the physical behaviour or state of the system being modelled (ibid.). In health, models are useful to 1) plan or evaluate interventions, especially when a controlled trial is not possible, 2) explore the underlying causes of health phenomena and drivers of epidemics, and 3) predict the occurrence of rare or future events from recorded intermediate points, perhaps embedded within a trial to inform interim analyses (e.g. [6]) [7].

An influential early model was developed by Bernoulli in 1760 to estimate the effectiveness of smallpox vaccination[8]. Bernoulli is considered the first author to study the benefits of vaccination through the use of mathematics[4], making a series of

simplifying assumptions to compare the long-term benefit of vaccination with the short-term risk of dying. Bernoulli made a number of simplifying assumptions to mathematically describe the spread of the pathogen in the population. Specifically, he split the population into those susceptible, infected, and immune to smallpox, and used (recently developed) calculus methods to describe the rates at which people became infected with smallpox. Per unit of time, people infected with smallpox die with a probability p , survive with the probability $(1 - p)$, and become infected at a rate of λ , a parameter which was later termed the force of infection[9].

Derivations of Bernoulli's methods, including the susceptible-infected-immune structure and description of time-invariant rates of change, are still applied in static models today, including in paper R2 in this thesis. Dynamic, nonlinear modelling was developed by Kermack and McKendrick to represent the spread of cholera in a three-compartment, susceptible-infectious-recovered, or SIR, model[10]. Nonlinearity was an important innovation to allow the rate of infection to be dependent on the number of those infected, how long they are infectious for, and the infectivity of a pathogen. This dynamic framework is useful for representing epidemics of pathogens with long incubation periods and changing populations of susceptible and infected persons, such as HIV, and can give a more accurate representation of the force of infection than static models[3]. A dynamic model is presented in results paper R4.

A range of model forms can be used to describe the processes associated with infectious diseases. There are advantages and disadvantages of each, and decisions around model structure and the level of complexity modelled should be made based on the decision question being modelled and the availability of data[4]. For example, simple static models are relatively easy to develop, can be transparent, need comparatively few data, and can give robust approximations that allow the identification of key factors that impact disease transmission[7, 11, 12]. These simple models may miss key features of

epidemics or nuances that are epidemiologically important. For example, static models assume a constant force of infection (or incidence), independent of the number of infectious individuals in the model or the coverage of preventative interventions. In reality, the greater the number of infectious persons, the greater the probability that an effective contact will be with an infectious person, meaning that a static model would underestimate incidence. By contrast, static models may overestimate incidence when preventative interventions are present as they will not account for reduced likelihood that a given individual is infectious [4, 13]. Where these aspects of disease spread are considered important to the spread of a pathogen, or the effectiveness of prevention/treatment interventions, dynamic models should be used to more accurately reflect these dynamics in the model.

Mathematical models can be characterised on four dimensions, as 1) individual or population based 2) deterministic or stochastic, 3) linear or nonlinear, and 4) static or dynamic[4, 7]:

- 1) Population-based models (e.g.[14, 15]) track average changes across groups by characterising compartments of the population without specifying the individuals involved and are largely used to examine population-level processes and trends. Yet infectious disease systems are fundamentally individual-based stochastic processes[16], and although population-based models can capture the average dynamics of the epidemic over time, they may miss important variation in individual-level risks, behaviours, and stochastic variation.
- 2) By contrast, individual-based models explicitly simulate the path of individuals over time through a model (e.g.[17]). Individual-based models offer more insight into individual-level behaviours and interactions and can include network structures, such as sexual mixing [7].

- 3) Deterministic models describe systems that are approximated for large populations and are fully described by a given set of parameter values with one solution. They are nearly always population-based models, and therefore share the weaknesses mentioned above in approximating individual-level dynamics. Stochastic models model individuals and are commonly used in small-scale epidemics or contexts where an outbreak may be largely due to chance[4]. They represent events with a certain probability and explicitly incorporate randomness into models(ibid.).

Not all processes are accurately described by stochastic models; for example representing the chance of small outbreaks beginning on hospital wards fit the framework well, whilst representing complex social mixing processes across larger populations do not. For larger epidemic (such as HIV), stochastic representations of system elements are often incorporated into population-based dynamic models through sensitivity analyses or, in some cases, Bayesian methods for choosing relevant parameter sets[4].

- 4) Linear models are static and represent parameters as constant, linear functions of environmental factors. Nonlinear models have parameters that vary according to a functional form of some of the variables in the model.
- 5) Dynamic models are used to describe changes in transmission risk over time because this risk depends on the number of infectious persons in the model. In static models, this risk is predetermined and exogenous to the model's state[4]. Dynamic models are, by nature, non-linear.

Mathematical models can give us perspectives on epidemics that we cannot obtain from statistical models of correlations or trends in data. In fact, mathematical models attempt to describe the underlying processes that cause these. In many cases, models are parameterised to fit the epidemiological indicators of a current epidemic before the impact of different control measures is simulated[4, 7]. Here, models are used to

estimate the potential impact of new or ongoing interventions, particularly when controlled trials are not possible, or population level impact is not measured. These models estimate the impact of alternative control approaches on distal outcomes of interest and help understand the impact observed, alongside assessing consistency with intermediate outcomes. Finally, modelling can help determine drivers of epidemics (e.g. commercial sex, pimps, sexual concurrency, acute phase of HIV[15, 18, 19]) to help design new interventions, and can evaluate unintended outcomes of interventions that may not be apparent from trial data.

When combined with data on the cost of interventions and averted health costs, and parameterised in common measures of benefit such as disability-adjusted life years (DALYs) averted, the cost-effectiveness of interventions can be compared to a willingness-to-pay (WTP) threshold[20], or to other candidate interventions[21]. Models can also be used to guide resource allocation within budget constraints.

Key considerations in the mathematical modelling of HIV

Mathematical models of HIV have been widely applied to understand how different epidemics have developed in different contexts. Models have been used since the early days of the HIV/AIDS epidemic to understand the spread of the virus among a certain population, in particular, its development into a generalised epidemic, with key contributions by Anderson and May, LePont and Blower, Lin et al., Busenberg et al., and Jacquez et al.[22-26].

More recently, models have been used to explore more detailed dynamics in the spread and control of HIV, estimate the cost-effectiveness of innovations in treatment and prevention, and to get a deeper understanding of how the epidemic can be controlled[27]. For example, models have been used to evaluate HIV prevention programmes by generating a counterfactual epidemic for the large-scale *Avahan*

intervention in India[14], to make a case for a universal test and treat approach for HIV elimination[28] and to show that new HIV prevention products may be a cost-effective way of spending finite health resources if targeted to specific geographical areas or structurally vulnerable groups[29].

R_0 in HIV models

Kermack and McKendrick's SIR model structure is still used, with minor adaptation, to describe the spread of many pathogens[3, 4]. HIV takes a susceptible-infected (SI) structure, because an infected person can only suppress the virus, naturally or through treatment, and does not fully recover. In an example of how the characteristics of the epidemic in question shape modelling methods, compartmental HIV models take this simple SI structure but incorporate a) complexity among infected individuals such as treatment status and viral load, and b) variations in risk-taking behaviours and cross-population mixing. This section details how these dynamics are formalised in an HIV model.

An important factor in these models is the value of the basic reproduction number, R_0 , which represents the transmissibility of a pathogen by the number of secondary cases produced by a single infection in a susceptible population[4]. For an epidemic to be sustained, R_0 must be greater than or equal to one. For the simplest model describing HIV transmission, R_0 can be characterised as:

$$R_0 = \beta cd \quad (1)$$

Where:

β represents the per-exposure transmission probability of HIV transmission;

c represents the rate at which new partnerships are formed in the population;

and

d represents the duration of infectivity for infectious persons.

R_0 is a simplistic characterisation of the complex factors that underlie these three parameters. Each of these has important implications for understanding the existence and persistence of HIV epidemics, and I discuss them in turn.

β , the per-exposure transmission probability of infection, varies according to the type of exposure. Table 1 presents estimates of β as summarised by the US Centers for Disease Control and Prevention (CDC) [30]. This table shows the HIV risk per 10,000 exposures, for a range of HIV transmission modalities. For example, in every 10,000 blood transfusions with HIV infected blood we would anticipate 9,250 HIV infections, whilst in every 10,000 unprotected sex acts between a HIV negative male and HIV positive female, we would expect four infections to occur. Three things are particularly notable from these numbers: 1) that risk may vary by gender, with heterosexual male-to-female transmission risk roughly double that of female-to-male transmission; 2) receptive anal intercourse is by far the riskiest activity relative to other sexual activity; and 3) that needle-sharing during injecting drug use has a relatively high transmission risk compared to sexual activity, except receptive anal sex.

Table 1: CDC summaries of estimated per exposure probability of acquiring HIV from an infected source, by exposure act

Type of exposure	Risk per 10,000 exposures
Blood transfusion	9,250
Mother-to-child transmission (untreated)	4,500
Receptive anal intercourse	138
Needle-sharing during injecting drug use	63
Insertive anal intercourse	11
Receptive penile-vaginal intercourse	8
Insertive penile-vaginal intercourse	4
Oral intercourse (receptive or insertive), biting, spitting, and throwing body fluids	Low or negligible

Table adapted from CDC data[30]

In most models estimating the preventative impact of interventions, the value of β is reduced by the effectiveness of a method in reducing HIV transmission. For example, male condom use has been shown to reduce HIV risk by 80%[31, 32]. For example, when a condom is used by an HIV positive male in a heterosexual vaginal sex act with an HIV

negative female, we model the probability of HIV transmission to be reduced from 0.0008 to $0.0008 \times (1-0.8) = 0.00016$. Conversely, male circumcision is estimated to reduce HIV female-to-male HIV transmission by around 50-60%[33-35]. The scale up of voluntary medical male circumcision has become an important part of HIV prevention programmes among men[36]. As described previously, PrEP is a promising new tool for HIV prevention despite concerns about variations in efficacy across populations and geographies. A recent systematic review[37] estimated that PrEP products have a 51% (95% CI: 27–67%) efficacy across all populations, though among women under the age of 25 PrEP was not found to be effective (point estimate 29% efficacy, 95% CI: -4 – 53%).

The parameter c represents the rate at which individuals form new sexual partnerships. The rate at which partnerships change, or are concurrent, is particularly important in HIV because infectivity rates are at their highest during the early stage of HIV infection when viral loads are extremely high – termed the acute or high viremia phase[38, 39]. The extent to which this drives incidence is debated, with Pilcher et al. suggesting that transmission in the acute stage leads to a high incidence rate among concentrated populations of people with many sexual partners before disease progression slows the spread into the general population or to lower-risk individuals [40]. However, a reanalysis of the limited data on infectivity during the acute stage of HIV infection by Bellan et al. indicates that this stage may be less important to epidemic development than first thought[41]. The most recent contribution to the debate, Volz et al. in 2013 [42], estimates that HIV positive persons are eight times more infectious during the first year of infection compared with chronic infection.

Assumptions around the acute stage of HIV infection are also important when considering d , the duration of infection for HIV. More recently, the discovery that consistent use of HIV treatment reduced the probability of onward transmission by around 96%[43] led to optimism that treatment as prevention could be an effective and

efficient mechanism to tackle the epidemic in populations that can use treatment effectively. A provocative modelling analysis by Granich et al.[28] showed that annual HIV testing of most adults, with immediate linkage to treatment for all positive persons, would dramatically reduce HIV incidence and potentially lead to elimination. Garnett and Baggaley[44] suggest that this strategy “would reflect public health at its best and its worst”, potentially reducing HIV-related morbidity and mortality at the cost of over-testing, over-treating and reducing the autonomy of individuals to choose care. Granich et al.’s model was one of twelve included in a systematic comparison by Eaton et al.[45], which showed that mathematical models were too optimistic in their estimation of the benefits of test and treat, particularly in the longer term. Although test and treat remains a fundamental part of the HIV response in many countries, it is now generally seen as part of a broader package of treatment and prevention services[46].

This scope of this thesis is to model the potential impact and cost-effectiveness of PrEP and other ARV-based HIV prevention products. In particular, it focuses on how different interventions may reduce the per-act probability of HIV transmission, β and, in paper R4, the rate at which new partnerships are formed, c . This thesis does not focus on factors affecting d .

In the next section, I describe the force of infection, with a particular focus on how protection is modelled in this framework.

Estimating prevention coverage

When combined, mathematical models and economics can give comprehensive insight into effective and cost-effective ways to tackle the HIV epidemic. Economic methods are used in all four results papers of this thesis and can be separated into two broad categories: microeconomic modelling and economic evaluation methods. Here I describe how, in this thesis, economic models can be integrated with mathematical models to

explore how the per-act transmission risk will be modified by the introduction of effective HIV prevention products.

$$\lambda = \beta I \quad (2)$$

Equation X.2 shows a simple representation of how to calculate the force of infection λ . The force of infection represents the risk that a susceptible person becomes infected during a given time period, and depends on β , as defined above, and I , a parameter representing the number of infectious persons in a given population.

Parameterising uptake

Where a preventative intervention is available, λ can be calculated by:

$$\lambda = \beta I(1 - \pi \varepsilon) \quad (3)$$

Where ε represents the efficacy of the intervention and π the proportion of the population using the intervention, such that λ is reduced by a factor representing the efficacy and use of the intervention. When implemented in HIV models, I represents a weighted average of infectivity, the proportion of the HIV positive population at each stage of disease, and treatment status.

π represents the coverage of HIV prevention products and is the product of uptake and adherence. Whilst efficacy data is relatively easy to obtain from published trials and meta-analyses of interventions (e.g.[37]), predicting the uptake of and adherence to new products is much more difficult. Terris-Prestholt et al.[47] noted that early modelling studies for ARV-based HIV prevention assumed very high levels of coverage, whereas more recent analyses make less optimistic assumptions. Yet, in the absence of data from the rollout of similar products or demonstration projects of new products, uptake parameters for models are generally obtained through expert opinion, trials, uptake of similar products, or by assumptions with minimal grounding in data (e.g.[48-51]).

This thesis builds on earlier work[52] by the author and supervisors to predict product uptake using the stated preferences of potential users, included in Appendix III. This methodological approach, alongside its strengths and limitations, is discussed in results paper R2 and the discussion in chapter 10.

Modelling risk compensation

Parameterising π is complicated further when there is more than one HIV prevention option available. Prior to the introduction of ARV-based products, the only effective methods of HIV prevention were male or female condoms, male circumcision, and abstinence or partner reduction. Although knowledge and use of female condoms is very low in South Africa[53], use of male condoms is relatively widespread and in 2012, self-reported condom use at last sex was 85% and 66% among general population men and women aged 15-24 years, respectively[54].

One approach to modelling the uptake of new prevention products is to assume that 1) the uptake of new products would be the same among condom users and non-users, or 2) that condoms would be used to the same extent after the initiation of prevention product use as they were before (i.e. no substitution).[55-57] However, it is possible that the introduction of PrEP could result in condom substitution, where PrEP users cease condom use when using PrEP. Some data from oral PrEP trials, largely among MSM populations, indicate that self-reported condom use did not change among PrEP users[58-61]. In contrast, a number of studies have detected increased STI rates among PrEP users than non-users, an objective indication of increased levels of condomless sex[62-65].

Prevention product coverage, in particular the extent of condom substitution, is critical in parameterising reliable transmission models. Despite this, only some models explicitly accounted for condom substitution or other forms of risk compensation. In 2003, Foss et al.'s model of condom substitution with microbicide use found substantive

benefits of reasonable (50%) uptake of microbicides among low condom users (25% of sex acts or less), but raised concerns if consistent condom users (75% of sex acts or more) substituted condoms for microbicide use[12]. An extension of this model for PrEP in 2017 by Grant et al. (currently under review) predicted that condom substitution could be tolerated among FSWs with lower levels of condom use before PrEP (<50% of acts) or where PrEP effectiveness is high (>75%). The authors also found that exposure to STIs, with subsequent increased susceptibility to HIV infection, would have very little impact on PrEP effectiveness (<1% change in results). Mitchell et al.[21] found that a 50% reduction in condom use by PrEP users was needed to negate the beneficial impact of PrEP. Punyacharoensin et al.[66] modelled scenarios of risk compensation among MSM PrEP users in the UK and found that PrEP effectiveness would be negated if the amount of condomless sex or sexual partners increased by around 50%, while projected decreases in HIV testing had little impact. Among MSM in the USA, Jenness et al.[67] estimated that full substitution away from condoms would lead to an 8% relative infection risk among PrEP users.

The literature shows that assumptions around risk compensation could be important in PrEP models. Despite this, the integration of parameters for the existence and magnitude of behavioural changes due to PrEP has not been driven by data or a strong theoretical justification. Instead, assumptions have been made within models as sensitivity analyses, for example exploring a 50% or 100% condom reduction after PrEP use[66], or the extent of condom substitution required to fully negate the impact of an intervention.

This thesis describes how a new methodological approach could be used to model prevention coverage. Paper R2 uses a DCE to predict prevention product uptake differentially among condom users and non-users. Paper R4 applies economic theory to the results of paper R3, which directly estimates changes in commercial sex act price and

condom use among PrEP users, to provide a more nuanced estimate of PrEP effectiveness.

Integrating economics and infectious disease modelling

Overview of economic methods used in this thesis

This thesis employs two economic methods: stated preference choice modelling using DCEs, and economic evaluation.

Economic evaluation is used in paper R2 which combines a simple impact model with a cost model to estimate the cost-effectiveness of MPTs. The approach taken in this thesis is outlined fully in the methods sections of the results papers. This section gives more extensive background to each without duplicating information.

Microeconomic methods

This section outlines the key theories underlying the microeconomic methods used in this thesis. I first outline some approaches used to research consumer preferences and demand, before justifying the use of the stated preferences in this research. Second, I briefly outline the theoretical foundations of the DCE approach to obtain stated preference data. Third, I present a brief discussion of the benefits and challenges in using DCEs to inform models of HIV prevention.

Consumer theory

Kelvin Lancaster's 1966 seminal paper "A New Approach to Consumer Theory" challenged the pervasive neoclassical theory of consumer demand, which was grounded in the assumption that consumers derive utility from the consumption of goods themselves. Lancaster's key contribution was to suggest that goods, per se, do not provide consumers with utility, but that the characteristics of goods in aggregate give rise to utility.

This may seem self-evident, but is an extension to the assumption of neoclassical theory that goods are non-divisible and intrinsically valuable. By describing the value of goods as the aggregation of their characteristics, Lancaster's theory allows the consideration

of goods' complementarity and substitutability. Complementary goods are those which are likely to be used together, for example, shoes and shoelaces – if the price of shoes goes up, we expect the demand for shoes to fall and subsequently the demand for shoelaces to fall as well. Sandals may be a substitute for shoes, where if the price of shoes goes up leading to a fall in quantity supplied, all else equal, the quantity of sandals purchased will go up.

The key contribution of Lancaster's theory in this thesis is to explore tradeoffs in greater depth. More than one good may share characteristics. For example, two different cars may be the same colour, which implies that a consumer's choice between cars of their preferred colour is strictly based on remaining differences such as speed or comfort. Furthermore, if we know how much consumers value certain characteristics of goods (their *shadow price*), we can predict the demand for new goods with similar attributes before they enter the market.

Demand for health and health services

Like any other good or service that provides utility, consumers demand good health. However, there are important limitations to using economic theory to describe choices in health contexts. Building on key limitations set out by Kenneth Arrow[68], Grossman's 1972 model of demand for health services[69] describes the demand for health care as a *derived* demand, whereby consumers do not gain utility from consumption of a health service itself but from the subsequent benefits to their stock of good health. Grossman's description of health as a stock, allocated at birth, allows the use of an economic framework to describe behaviours that increase or diminish that stock according to the relative utility that actions give us. For example, a smoker can be said to gain more utility through the immediate consumption of a cigarette than from the subsequent reduction in long-term health stock.

Preference elicitation methods

Where possible, economists observe behaviour and use statistical methods to understand why market participants behave in particular ways. Information gathered from observing real-life behaviour is referred to as *revealed preference* (RP) data, as preferences are revealed through a person's actions[70, 71].

RP data can be limited or non-existent for consumers who act to maximise their health through consuming products that can improve (or maintain) their health, such as surgery[72, 73] or preventative products[74]. Such consumers rarely face market prices for their consumption due to public or private insurance and are subject to agency relationships between patients and providers where decisions are unlikely to solely reflect patient preferences[70, 71, 75]. There are often little or no revealed preference data available on consumer demand for new technologies or interventions[74-77].

Stated preference methods

Where revealed preference data are not available, economists have turned to *stated preference* (SP) methods where potential consumers (or those impacted by a policy or intervention) are asked *what they would choose*, as opposed to *what they chose*. The hypothetical nature of this method allows researchers to explore new or proposed products or situations where a convenient real-world experiment does not exist[70, 75, 78]. Health practitioners have been enthusiastic adopters of SP techniques, which were first used in transport[79] and environmental[80] economics.

An important limitation of stated preference methods is the potential for hypothetical bias, where the choices that participants make in stated preference exercises are different to the choices that they would make in reality. This is particularly important for this thesis where DCEs are used to predict uptake in impact and cost-effectiveness models. To acknowledge the potential for hypothetical bias, this thesis 1) conducts a systematic review to assess the external validity of DCEs to predict health choices,

presented as chapter 4, which concludes that DCEs have reasonable predictive validity to predict health choices; and 2) where DCE predictions are used in models, the large degree of uncertainty in their predictions is incorporated into sensitivity analysis with wide parameter ranges.

Potential stated preference approaches

This section describes two stated preference approaches that were considered for use in this thesis but were not chosen: contingent valuation and best-worst scaling.

Contingent valuation (CV) involves asking respondents for their willingness to pay, or willingness to accept, certain conditions. It commonly uses open-ended questions (*how much would you be willing to pay for \$X?*) or categorical questions (*would you be willing to pay \$X?*), although other bidding games or dichotomous choice tasks have been used[81]. Although widely applied in transport, environmental and some health contexts, a large body of evidence suggests that hypothetical bias in CV studies can lead to a substantial overstatement of willingness to pay values[82-85]. Importantly for the objectives of this thesis, while CV could be used to value the importance of different attributes of prevention products, predicted probability analysis could not be carried out to predict product uptake.

Best-worst scaling (BWS) is a relatively innovation for eliciting stated preferences. The approach is attractive for researchers as experiments gather more data *per task* than traditional DCEs, and is argued to be less cognitively burdensome as participants do not have to consider between sets of alternatives[86-91]. There are two common applications of BWS, the *profile case 2* is most commonly applied, while the *best-worst DCE case 3* is more similar to the traditional DCE. Figure 1 shows stylised examples of these compared to a traditional DCE.

Recent literature has indicated that using the BWS profile case 2 in health can obtain similar results to other preference elicitation methods, including DCEs [92], and studies

require a smaller sample size due to the greater quantity of information obtained per response, alongside the reduced complexity of tasks[87, 93]. However, like CV, BWS profile case 2 exercises do not allow for the prediction of behaviours via predicted probability analysis, and only allow estimation of conditional demand, i.e. preferences based on wanting to use a given service or product.

Figure 1: Types of best-worst scaling in comparison to DCE

"Traditional" Discrete Choice Experiment		
	Act A	Act B
Price	500 Rand	200 Rand
Protection	No Condom	Condom
Type of sex	Vaginal	Vaginal
Other HIV prevention products used?	HIV risk reduced by 87%	HIV risk reduced by 0%
<i>Please pick the transaction you would prefer</i>		
	Act A	Act B
	✓	

Best-Worst Scale - Profile Case 2			
<i>Please tick the best and worst characteristics of the following transaction:</i>			
		Best	Worst
Price	500 Rand		
Protection	No Condom		✓
Type of sex	Vaginal		
Other HIV prevention products used?	HIV risk reduced by 87%	✓	

Best-Worst Discrete Choice Experiment - Case 3			
	Act A	Act B	Act C
Price	500 Rand	200 Rand	500 Rand
Protection	No Condom	Condom	No Condom
Type of sex	Vaginal	Vaginal	Vaginal
Other HIV prevention products used?	HIV risk reduced by 87%	HIV risk reduced by 0%	HIV risk reduced by 0%
<i>Consider each of the three acts described above. Which would you describe as the best? Which would you describe as the worst?</i>			
	Best	Worst	

Discrete choice experiments (DCEs)

The most popular method of stated preference elicitation in recent health literature has been the DCE[94, 95]. DCEs require participants to pick one of two or more options, with each being described by a set of characteristics. Respondents are presented with a sequence of choice tasks (normally around 10), and their choices analysed to estimate a set of preferences as implied by a particular indirect utility function[74]. Estimates are then used to measure which attributes are important to people, or (when the DCE includes an opt-out alternative) predict future behaviour, a method commonly used to predict product market shares[87].

DCEs are analysed using a discrete choice modelling framework as proposed by McFadden[96, 97]. Importantly, when opt-out (or status-quo) alternatives are included in DCE designs, the demand for new alternatives can be predicted relative to that of existing products – the estimation of this unconditional demand makes DCEs useful tools for predicting health behaviours, and provides insight that BWS methods do not, and that CV does only with substantial complexity. Further considerations in the design of the DCEs used in this thesis are described in the method Chapter.

Four discrete choice models are used in this thesis: multinomial logit, mixed multinomial logit, nested logit, and latent class. These models and their estimation are described fully in each results paper, alongside their comparative advantages and disadvantages, and are not duplicated here.

Economic evaluation

Drummond et al.[98] define an economic evaluation as “the comparative analysis of alternative courses of action regarding both their costs and consequences”. Where resources are finite and not allocated by a market, as in the case of health services, provision is left to governments who require information on the expected benefit from investments alongside their value for money. Studies which compare the costs and benefits of different health interventions are referred to as economic evaluations.

Morris et al.[73] argue that the development of economic evaluation techniques to measure efficiency in non-market health settings is “perhaps the main contribution economics has made to decision making in health services”. Modern economic evaluation methods are largely based on cost-utility analyses and a) capture a range of health benefits regarding quantity and quality of life, b) use standardised measures to allow comparison of costs and consequences across health areas, and c) have become mainstream methods of service commissioning in the UK and elsewhere.[73, 98]

The economic evaluation methods used in this thesis are described fully in results paper R2 and its supplementary material and are not duplicated here. Instead, I give a brief overview of the literature that assesses the cost-effectiveness of ARV-based HIV prevention products.

Where economic evaluations are based on cost-utility analyses, because costs and benefits are estimated with different units, results are presented as incremental cost-effectiveness ratios (ICERs):

$$ICER = \frac{cost_{intervention} - cost_{comparator}}{benefit_{intervention} - benefit_{comparator}} \quad (4)$$

Observed cost data are often included in economic evaluation models through a separate cost modelling process where assumptions are made around the scale of an intervention, and its impact on the costs of labour and commodities[99].

In low and middle-income contexts, best-practice economic evaluations quantify benefit as the number of DALYs averted by an intervention over that of a defined comparator[100, 101]. DALYs are a composite measure of quality and quantity of life. Because they are not specific to disease outcomes, they allow comparison of cost-effectiveness within and across disease areas. For example, DALYs allow direct comparison between interventions a) to improve HIV treatment or prevention services and b) seeking to avert HIV or malaria infections[73]. To assess cost-effectiveness, the ICER of an intervention is compared to a governmental WTP threshold which, in theory, represents the opportunity cost of disinvesting from existing health services to re-direct resources to the new intervention[73, 98]. In low- and middle-income countries, World Health Organization (WHO) thresholds of averting one DALY for one to three times per capita income have been widely used. However, this method has received criticism for not reflecting real-world funding decisions or the opportunity costs of healthcare spending[20, 102]. Therefore, in paper R2 we use the lower-bound of the South African WTP threshold of \$1,175 estimated by Woods et al.[20], which is markedly lower, and hence more conservative, than the WHO thresholds. This threshold aims to reflect better the opportunity cost to the South African health system of investing in new health technologies by considering the health forgone because other interventions cannot be provided.

Cost-effectiveness analyses for ARV-based HIV prevention

Since the development of microbicides for HIV prevention, impact and cost-effectiveness modelling has sought to estimate the potential epidemiological and economic value of ARV-based prevention methods. Terris-Prestholt et al.[103] showed that a microbicide gel would be cost-effective under product effectiveness assumptions that were later proven ambitious[104]. Later evidence demonstrating that microbicides have poor effectiveness in many groups, alongside the development of oral PrEP products, has

shifted focus away from gel-based products to oral or intravaginal ring-based topical products, which are not dependent on coital use[105].

Evidence demonstrating a lack of protection from microbicide gels has led to recent cost-effectiveness work focusing on estimating the cost-effectiveness of oral PrEP. A systematic review in 2013 by Gomez et al.[29] identified 13 studies modelling the cost-effectiveness of oral PrEP, concluding that it “has the potential to be a cost-effective addition to existing HIV prevention programmes in some settings” but noting that estimates are sensitive to model assumptions of PrEP cost, epidemic context, and PrEP programme coverage.

Since 2013, modelling work among non-MSM populations has focused on characterising heterogeneity in the cost-effectiveness of PrEP, specifically studying populations of pregnant women[106], the HIV-negative partner in serodiscordant relationships[107, 108], and other high-risk female groups[48, 50, 51]. Due to issues with product adherence, focus has begun to turn towards longer-acting ARV-based prevention which requires less frequent use. One analysis explores the cost-effectiveness of injectable products[109], one study assesses the value of a multipurpose intravaginal ring for HIV prevention[110], and one study estimates the cost-effectiveness of introducing multiple ARV-based HIV prevention products[49]. To date, no study has estimated the cost-effectiveness of a range of MPT products.

Implications for thesis

Justification of DCE use

Given that this thesis aims to explore the potential impact of HIV prevention products that were not available at the time of conducting the research (and remain inaccessible to many), no revealed preference data were available. Although some trial data are available, we would require data from a programme introducing a range of MPT products where users could freely opt-in or opt-out of product use, which is not the design of successful clinical trials.

To explore the impact of prevention products on the market for commercial sex, the ideal study design would be to randomise some women to receive PrEP and some to not. This was not possible given funding constraints, and would likely have been unethical given that PrEP has been shown effective in many groups.

The ability of DCEs to predict the unconditional demand of products that do not exist, including substitution away from current condom use, makes them flexible and attractive tools to help inform infectious disease models. Both DCEs used in this thesis rely on the work of Lancaster [111] as they decompose choices into constituent attributes, allowing us to explore how respondents trade-off between positive and negative aspects. Grossman's model of health as a stock held over a lifetime also informs our modelling of prevention products uptake as products are unlikely to confer immediate utility to a user. Instead, consumption of prevention products reduces the risk of a substantial, negative impact on health stock by preventing HIV infection.

Modelling and cost-effectiveness

All published studies identified have shown that ARV-based prevention could be cost-effective, at least among some population groups or under favourable cost-assumptions. However, a consistent theme across the literature is that cost-effectiveness will depend on a number of highly variable factors, including: the extent to which antiretroviral

treatment is scaled up, the costs of new products, the extent to which products are used consistently by those at risk, and the extent to which existing programmes (including voluntary medical male circumcision (VMMC) and condom promotion) can be effectively scaled up. Only one study estimates the cost-effectiveness of an MPT[110] and, similarly, one study the cost-effectiveness of a range of different ARV-based prevention options[49]. Thus, this chapter identifies a key gap in the modelling and cost-effectiveness literature relating to the modelling of MPTs, which Paper R2 seeks to fill by assessing the potential cost-effectiveness of a range of candidate MPTs.

The next chapter presents a literature review on the economics of sex work, the other key theme of this thesis.

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Chapter 3: Economic influences on female sex worker choices: A literature review

Overview of paper

This chapter presents a review and synthesis of the literature exploring economic determinants of the choices and behaviours of female sex workers. This paper is being finalised for submission.

The review proposes a conceptual framework which is used later in the thesis to identify important determinants of FSW risk and choices that the introduction of effective HIV prevention products might change. These form the long list of attributes which were refined for the FSW DCE as presented in paper R3.

Although the review identifies some influences on the risks that FSWs face and the choices they make, the nature of the DCE study means that findings regarding individual-level influences on choices are used in the attribute selection process.

The paper is formatted to be submitted to *Economics and Human Biology*, and implications for this thesis are presented as a separate section, after the paper's reference list.



RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Matthew Quaife
Principal Supervisor	Fern Terris-Prestholt
Thesis Title	Using stated preferences to estimate the impact of new HIV prevention products in South Africa

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	
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Please list the paper's authors in the intended authorship order:	Quaife M
Stage of publication	under preparation.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	
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Student Signature: _____

Date: 17/7/17

Supervisor Signature: _____

Date: 17/7/17

Economic influences on female sex worker choices: A literature review

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Abstract

Women who engage in commercial sex, or female sex workers (FSWs), face daily threats to their health and wellbeing. Although a great deal of literature has focused on the epidemiological determinants of FSW and client behaviour, economic work has also explored how operating in a competitive market may influence choices and behaviours. Although relevant to epidemiological and biomedical research, there is little crossover between literatures and economic work has not been comprehensively reviewed or synthesised to date. 4,470 potentially relevant studies were identified, of which 56 were included in a narrative synthesis. Results are presented through the construction of a conceptual framework, which categorised influences into act- and individual-level factors, system-level factors, and exogenous factors. There is strong evidence suggesting that economic factors play a substantive role in the choices of FSWs and client. These factors should be explicitly incorporated within epidemiological frameworks of risk.

Introduction

There are a wide range of structural and social factors which influence whether and how female sex workers (FSWs) can protect themselves from acquiring HIV or STIs. The decisions of women who sell sex are also affected by operating in an environment where economic factors, such as financial incentives or market competition, can substantially affect the choices that FSWs make which ultimately form behaviours[1-5]. This review aims to inform a conceptual model of how economic and market forces can impact these choices, in addition to biological, social, and structural factors. It summarises and critically appraises the economic literature which has sought to explain how market influences might affect commercial partnerships, and highlights gaps where further research is needed.

Early economic literature on sex work generally took one of two approaches, either to draw out the similarities of the sex work industry with other formal sectors or professions (for example [6, 7] cited in Cunningham and Kendall[8]), or study it as a form of criminality following economic work on relationship between criminality and human capital (for example [9-11]). Later work complements this market-level approach by exploring the role of act- and individual-level characteristics on FSW and client choices[12-14].

Shannon et al.'s systematic review of structural drivers of HIV risk among FSWs[5] illustrates the complexity of exploring HIV prevention among FSWs and documents the range of structural factors identified as influencing the likelihood a FSW will acquire HIV. Economic factors are considered to influence HIV risk among FSWs through *macrostructural* factors, referring to the vulnerability which women may face due to economic arrangements at a societal level, for example through poverty or income insecurity, power imbalances between FSWs and clients or non-commercial partners, and regulatory frameworks[15-18]. Further *economic features* are noted as influencing

the work environment, an acknowledgement that economic factors at the individual level also play an influential role in exposure to HIV and other health risks[19-21].

Review Methods

Aims

This review aims to:

1. Comprehensively review studies which identify economic influences on the choices of female sex workers,
2. Describe and synthesise common themes in the literature,
3. Critically appraise and identify gaps in the literature on the economics of sex work.

Inclusion and Exclusion Criteria

The scope of the review was deliberately broad. We sought to identify any published work describing economic influences on FSW choices, whether looking at financial incentives for different types of risk behaviour, or more generally the organisation and dynamics of the sex work market. This meant that papers exploring either the extensive (entry into sex work) or intensive (decisions on how much of what sex to supply) margin of the industry were considered. We consider any published study between 2000 and 2016. Both theoretical and empirical work was included.

Papers were excluded if they were only published in conference abstract form, not published in English, or only considered male sex-workers. Papers which only considered transactional sex (i.e. where payment is through gift-giving or other non-monetary means) were not considered.

Literature Search Methodology

It was identified early in the literature search that the language used to describe analyses of economic factors affecting sex-work varied substantially between journals of different fields, notably between applied economic and public health publications. Therefore, to capture differences in terminology, a parsimonious search strategy was designed to be more sensitive than specific. This meant that more irrelevant studies needed to be removed by hand, however, some papers were identified that a more restrictive strategy might have missed. Search terms were developed starting from the broad research question: “How do economic factors affect FSW choices?”, and divided into two concepts as shown in Table 1. Searches were run with the Boolean AND term between these concepts. Additional concepts to restrict the scope of searches (for example, to health or risk behaviours) were not included to avoid the omission of potentially relevant articles and to maintain the wide scope of the review.

Where available, MeSH terms were used to identify articles missed in synonym searches. An iterative snowballing strategy was employed throughout where the references of relevant papers were examined for any potentially useful papers or search synonyms. In addition, studies citing included papers were obtained through Google Scholar and screened for relevance. Terms were applied to the EconLit, Science Direct, Medline, and EMBASE databases so that both economic and public health literatures were investigated.

Table 1: Search strategy

Concept	Search Term
Female sex workers	(female AND sex AND work*) OR FSW OR prostitute*
Economic factors	Market OR compet* OR incentive* OR price* OR wage* OR income OR compensat*

Synthesis

Articles are synthesised through a narrative overview, before allocation to three categories to synthesise key themes in the literature: act-level factors, system-level factors, and exogenous factors. These categories form the basis of a conceptual framework.

Act-level factors are characteristics of the act, client, or FSW that may affect the agency and ability of FSWs to make optimal choices. Included in this category are studies exploring the determinants of act price, for example work drawing on the economic theory of compensating differentials, which explains the dependence of wage rates on risk or unpleasantness of a job. Applied in labour economics across many industries and contexts[22-26], compensating differentials stem from the work of Adam Smith[27]:

“The whole of the advantages and disadvantages of the different employments of labour and stock must, in the same neighbourhood, be either perfectly equal or continually tending to equality”. (Smith, 1776. Book I, p. 111)

In the context of heightened economic and structural inequities in many countries, FSWs may be highly financially dependent on sex work to support themselves and their families [28-30]. Therefore, we would expect act price (an *advantage*) to compensate sex workers fully for the *disadvantage* of bearing risk or unpleasantness in their work. Similarly, if HIV prevention products reduce the risk of providing services, we would expect the premium to fall.

System-level factors are influences which are driven by the socio-legal framework within which FSWs operate, and this category includes potentially violent or exploitative relationships with clients or police and vulnerabilities due to the illegality of buying or selling sex commercially. FSWs often report violence and intimidation by clients and the police, with experience of violence strongly associated with inconsistent condom use and lower levels of participation in HIV and STI prevention activities[15, 18, 31]. Studies

which investigate competition between sex workers and market structure are also included in this category.

Exogenous factors are unrelated events or factors occurring outside of the commercial sex market, but which affect the decisions of FSWs and clients. For example, drought, conflict, or political instability may induce more women to engage in commercial sex due to a lack of other income generating alternatives.

Results

Overview of included studies

In total, 8,870 records were identified in searches, 17 records added through the snowballing process, and 3,831 duplicates removed. 56 papers were included in the review after full-text sifting. Notably, 9 of the papers identified via snowballing came from a recently published book, *The Oxford Handbook of the Economics of Prostitution*, which did not appear in database searches. Chapters of this book were omitted if they solely presented data published in paper form elsewhere. Details of the review process are given in the PRISMA diagram in Figure 1, and all included studies listed in table 2. Eleven studies were carried out in the USA and Canada, ten in sub-Saharan Africa, and seven in Asia and in Europe.

Although some papers were strictly theoretical contributions, the majority of models were tested empirically in a single or later publication. The structure and scope of many models sought to answer a specific policymaking question, for example estimating the impact of deregulation on sex work[13, 32], or the impact of political instability on the dynamics of commercial sexual behaviours[33].

We found no robust economic research into commercial sex until 2003, which Alberg and Jensen attribute to difficulties in collecting reliable data from FSW or client populations[34]. Figure 2 illustrates the publication of studies over time, with 2016

disproportionately represented due to the publication of *the Oxford Handbook of The Economics of Prostitution*. We observe a trickle of papers pre-2009, before an increase in work between 2010 and 2016.

In general, the tone of the literature has changed over time, and later work presents a complex, more nuanced, and less value-laden view of sex-work than earlier research. Edlund and Korn developed the first theoretical model of sex work, and postulate that female career trajectories are limited to either housewifery or sex work[1] (generously described elsewhere as an “unsatisfactory” assumption[35]), whilst Cameron’s book title *The Economics of Sin*, provides insight into the value judgements some economists make about sex work[4]. By comparison, more recent work – notably all studies by authors Cunningham, Gertler and Shah – implicitly assumes agency on the part of sex workers at the extensive and intensive margins, albeit with different negotiating power than clients. Considerations of heterogeneity in sex work across individuals and geographies is a growing elem

Figure 1: PRISMA diagram of review process

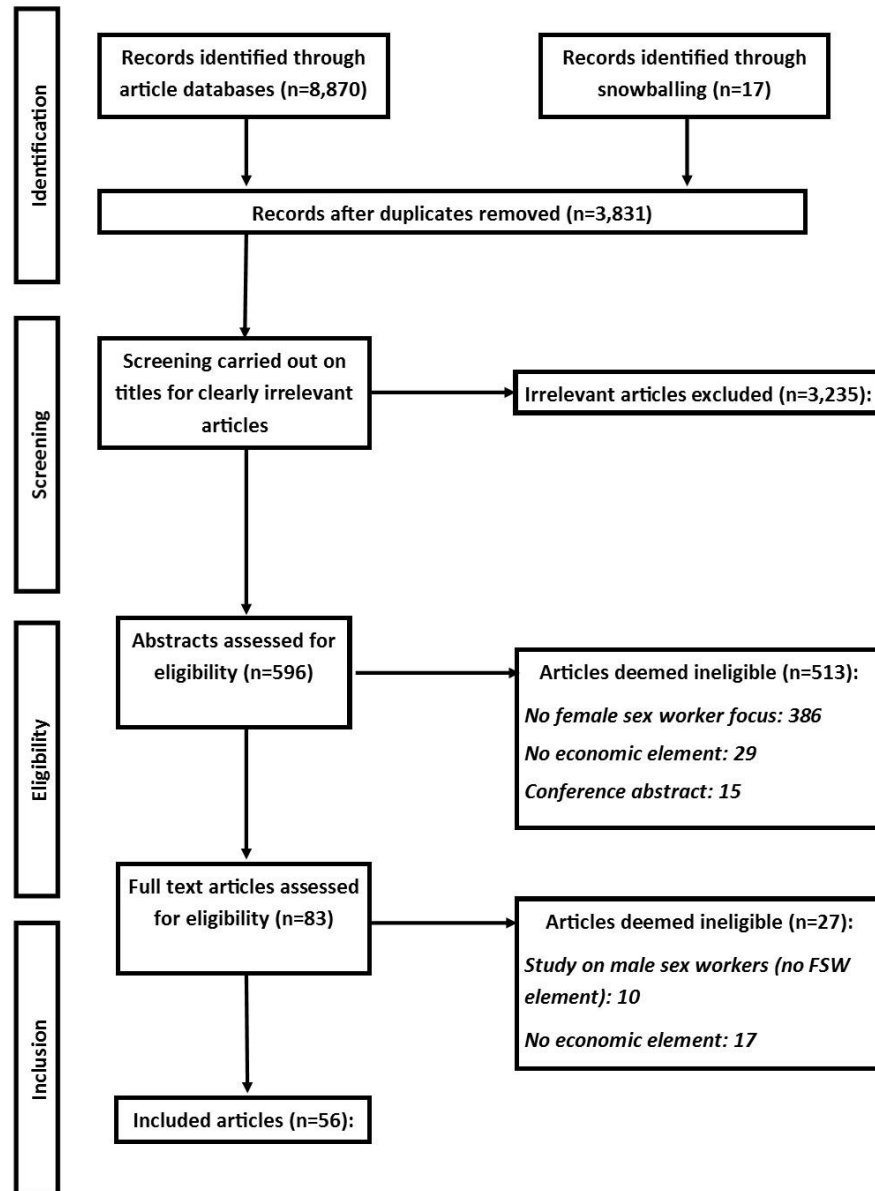


Table 2: Summary of included studies

Author	Year	Title	Journal	Act level pressures	Systemic risks	Exogenous factors	Sample size	Location
Empirical								
Adriaenssens and Hendrickx [36]	2012	Sex, price and preferences: accounting for unsafe sexual practices in prostitution markets	Sociology of Health and Illness	X			7,451	Netherlands, Belgium
Ahlburg and Jesnsen [34]	1998	The Economics of the Commercial Sex Industry and its Implications for HIV/AIDS Prevention Policies	Book chapter		X		SA*	Sub-Saharan Africa
de Araujo [37]	2016	HIV/AIDS and Commercial Sex Work in the Developing World	Book chapter	X			SA*	Sub-Saharan Africa
Arunachalam and Shah [38]	2008	Prostitutes and Brides?	American Economic Review: Papers & Proceedings	X		X	4,100	Ecuador, Mexico
Arunachalam et al. [39]	2012	The Prostitute's Allure: The Return to Beauty in Commercial Sex Work	The B.E. Journal of Economic Analysis and Policy	X	X		4,100	Ecuador, Mexico
Arunachalam et al. [40]	2013	Compensated for Life: Sex Work and Disease Risk	Journal of Human Resources	X	X		2833	Ecuador
Cameron [41]	2016	Empirical Analysis of the Impact of Legal Status on Versatility and Efficiency in Prostitution Markets	Book chapter	X	X		SA*	UK
Chang and Weng [42]	2012	What is more important for prostitute price? Physical appearance or risky sex behavior?	Economic Letters	X			140	Taiwan
Cunningham [43]	2011	Monopolistic competition with product differentiation in prostitution markets: explaining the returns to BMI	Working paper	X			94,000**	USA

Author	Year	Title	Journal	Act level pressures	Systemic risks	Exogenous factors	Sample size	Location
Cunningham and Kendall [44]	2011	Prostitution 2.0: The Changing Face of Sex Work	Journal of Urban Economics	X			94,000**	USA
Cunningham and Kendall [45]	2014	Prostitution, Education, and Moonlighting: A Demonstration of the Importance of Fixed and Variable Costs in Sex Worker Labor Supply	Working paper	X			685	USA
Cunningham and Kendall [46]	2014	Using Political Conventions to Estimate the Responsiveness of Prostitution Labor Supply	Working paper	X	X		SA***	USA
Cunningham and Kendall [47]	2016	Prostitution Labor Supply and Education	Working paper	X		X	685	USA
Cunningham and Kendall [48]	2016	Examining the Role of Client Reviews and Reputation within Online Prostitution	Book chapter	X			72,104**	USA
de la Torre et al. [49]	2010	Premium Sex: Factors Influencing the Negotiated Price of Unprotected Sex by Female Sex Workers in Mexico	Journal of Applied Economics	X			1,029	Mexico
de Walque [50]	2014	Coping with risk: the effects of shocks on reproductive health and transactional sex in rural Tanzania	Working paper	x			1,076	Tanzania
Dupas and Robinson [51]	2012	Simulating the impact of regulation changes on the market for prostitution services	European Journal of Law and Economics		X	X	586	Kenya
Ebstein and Sharygin [52]	2016	The (hidden) costs of political instability: Evidence from Kenya's 2007 election crisis	Journal of Development Economics	X			SA*	China
Edlund, Engelberg, and Parsons [53]	2009	The Wages of Sin	Working paper	X	X	X	40,000	USA, Canada
Egger and Lindenblatt [54]	2015	Endogenous risk-taking and physical appearance of sex workers	European Journal of Health Economics	X			2,517	Germany
Elmes et al [55]	2014	The Price of Sex: Condom Use and the Determinants of the Price of Sex Among Female Sex Workers in Eastern Zimbabwe	Journal of Infectious Diseases	X			311	Zimbabwe

Author	Year	Title	Journal	Act level pressures	Systemic risks	Exogenous factors	Sample size	Location
Gertler and Shah [32]	2005	Risky Business: The Market for Unprotected Commercial Sex	Journal of Political Economy		X		1,029	Mexico
Gertler, Shah and Bertozzi [14]	2011	Sex work and infection: what's law enforcement got to do with it	Journal of Law and Economics	X			2,914	Ecuador
Hakim [56]	2015	Economies of Desire: Sexuality and the Sex Industry in the 21st Century	Economic Affairs	X			SA*	Europe, USA
Holt, Blevins, and Fitzgerald [57]	2016	Examining the Economics of Prostitution using Online Data	Book chapter	X			1,844**	
Islam and Smyth [58]	2012	The Economic Returns to Good Looks and Risky Sex in the Bangladesh Commercial Sex Market	Economics of Gender	X			283	Bangladesh
Johnston et al. [59]	2010	Offer of financial incentives for unprotected sex in the context of sex work	Drug and Alcohol Review	X			232	Vancouver, Canada
Kwan [60]	2016	Decriminalizing Indoor Sex Work: Effect on Quantity of Transactions	Thesis. University of California, Berkely	X	X		238,501**	Rhode Island, USA
Levitt and Venkatesh [12]	2007	An empirical analysis of street level prostitution	Working Paper	X			4,400	Chicago, USA
Li et al. [61]	2015	Does Competition Eliminate Discrimination? Evidence from the Commercial Sex Market in Singapore	NBER Working Paper		x		176	Singapore
Manda [62]	2013	Bang for Your Buck: STI Risk and Pregnancy Risk as Sources of the Price Premium for Unprotected Sex	Working Paper	X			192	Kenya
Mannberg [63]	2011	Risky Sex in a Risky World: Sexual Behavior in an HIV/AIDS Environment	The Scandinavian Journal of Economics	X			SA**	Sub-Saharan Africa
Moffatt and Peters [64]	2004	Pricing Personal Services: An Empirical Study of Earnings in the UK Prostitution Industry	Scottish Journal of Political Economy	X			998+	UK
Mondal and Gupta [65]	2013	How costly is safe sex? An economic analysis of the commercial sex market in India	Global Health Perspectives	X			5,301	India

Author	Year	Title	Journal	Act level pressures	Systemic risks	Exogenous factors	Sample size	Location
Muravyev and Talavera [66]	2013	Unsafe sex in the city: Risk pricing in the London area	European Economic Association and Econometric Society	X			1,580	London, UK
Ntumbanzondo et al. [67]	2006	Unprotected intercourse for extra money among commercial sex workers in Kinshasa, Democratic Republic of Congo	AIDS Care	X			136	Kinshasa, DRC
Peng [68]	2016	Economic Theories and Empirics on the Sex Market	Book chapter	X	X			
Quast and Gonzalez [69]	2016	Sex Work Regulation and Sexually Transmitted Infections in Tijuana, Mexico	Health Economics		X		SA*	Mexico
Rao et al. [3]	2003	Sex workers and the cost of safe sex: the compensating differential for condom use among Calcutta prostitutes	Journal of Development Economics	X			608	Calcutta, India
Robinson and Yeh [33]	2011	Transactional Sex as a Response to Risk in Western Kenya	American Economic Journal: Applied Economics	X			192	Kenya
Robinson and Yeh [70]	2012	Risk-Coping through Sexual Networks: Evidence from Client Transfers in Kenya	Journal of Human Resources			X	192	Kenya
Sachsida and Moriera [71]	2010	A theory of prostitution	Economia e Desenvolvimento	X		X	151	Brasilia, Brazil
Shani and Shankar [72]	2016	The Details Are in the Fine Print: Sex Work, Sex Workers, and Definitional Complications of Identity	Book chapter	X			3,424	
Sohn [73]	2016	Men's Valuation of Temporal Proximity to Female Virginity: Evidence from Prostitutes	Deviant Behaviour	X			8,817	Indonesia
Willman[74]	2010	Risk and reward in Managua's commercial sex market	Journal of Human Development and Capabilities	X	X		138	Managua, Nicaragua
Theoretical								
Albert, Gomez and Franco [75]	2007	Regulating Prostitution: A Comparative Law and Economics Approach			X			

Author	Year	Title	Journal	Act level pressures	Systemic risks	Exogenous factors	Sample size	Location
Cameron [4]	2002	Economics of Sin: rational choice or no choice at all?	Book chapter		X			
Della Guista, Di Tomasso, Strom [76]	2007	Who is watching? The market for prostitution services			X			
Edlund and Korn[1]	2002	A Theory of Prostitution	Journal of Political Economy		X			
Farmer and Horowitz [77]	2013	Prostitutes, Pimps, and Brothels: Intermediaries, Information, and Market Structure in Prostitution Markets	Southern Economic Journal		X			
Immordino and Russo [78]	2015	Regulating prostitution: A health risk approach	Journal of Public Economics		X			
Immordino and Russo [79]	2016	Prostitution Policy	Book chapter		X			
Lee and Persson [80]	2016	Bargaining, Coercion, and Entry in Prostitution Markets: Implications for Prostitution Law	Book chapter		X			
Peppet [81]	2012	Prostitution 3.0	Iowa Law Review		X			

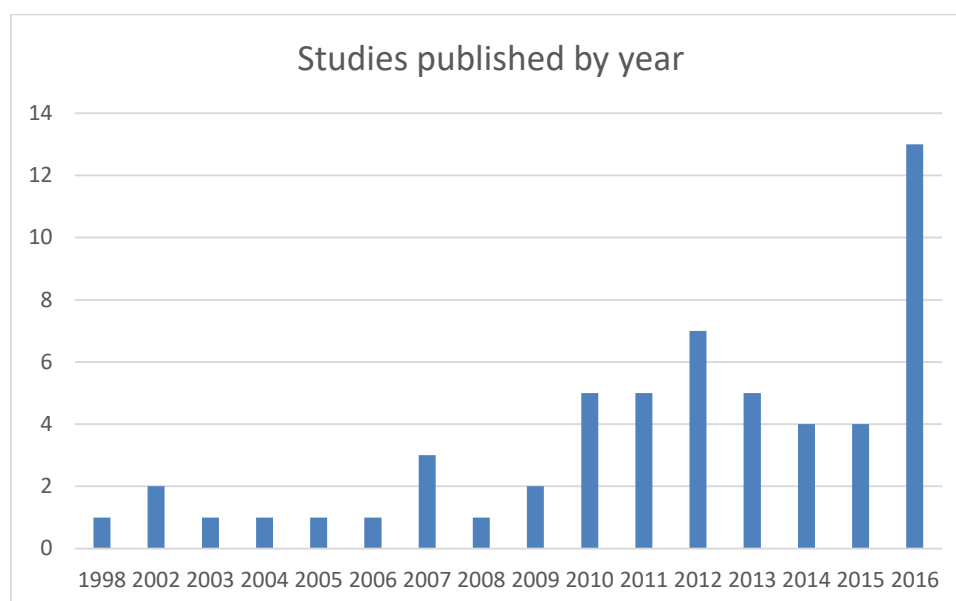
SA*: Secondary analysis of large household survey/epidemiological data

** Data taken from sex work review website

SA***: Secondary analysis of number of adverts posted on solicitation websites

+: transaction-level data, number of individuals not listed

Figure 2: Number of included studies by year published



Synthesis of economic factors influencing FSW choices

Papers are presented and synthesised by theme: 1) act- and individual-level factors, 2) system-level factors (further split into subcategories of decriminalisation, the extensive margin, and market structure), and 3) exogenous factors. Although largely mutually exclusive, when papers explore cross-category themes, they are included in all relevant sections.

Act- and individual-level factors

Work explaining the determinants of act price made up a substantial proportion of the literature, with 40 studies (72%) exploring act- or individual-level factors[3, 12, 14, 33, 36-49, 51-59, 61-65, 67, 68, 70-74]. Within this, the impact of condom use on the price of acts has been an important strand of research [3, 12, 14, 33, 36, 39, 40, 42, 43, 45, 47, 49, 51, 54, 55, 58, 59, 61, 62, 64-67, 71, 73, 74]. The remaining literature in this category explores different pricing dynamics in the market for commercial sex, setting price as a dependent variable and exploring correlations with a range of factors including: interviewer-assessed FSW sociodemographic characteristics, interviewer-assessed

attractiveness, time and place of work, client characteristics, industry experience, and type of acts supplied (37, 38, 41, 44, 46, 48, 52, 53, 56, 58, 59, 57, 63, 65, 68, 70).

Rao et al.'s seminal study [3] first applied the principle of compensating differentials to sex work by equating the disutility borne by a FSW in providing unprotected sex with the additional fee paid by the client. This study was the first to present convincing evidence of the existence of financial incentives in sex work, and a large empirical literature has since developed exploring variations in price, and defining the presence and magnitude of this *condom differential*.

After Rao et al, the study most notable in advancing empirical research in the field was Gertler, Shah and Bertozzi[14], who were the first to apply concepts of game theory to the bargaining process between a FSW and a client. The authors use qualitative research to develop a Roth-Nash bargaining framework, which suggests that the magnitude of the price premium for unprotected sex depends on client disutility from condom use, FSW disutility from unprotected sex, and bargaining power between the two parties. The authors' theoretical model is convincing, and is backed up empirically through a FSW fixed-effects regression estimating a 23% price premium for unprotected sex, increasing to 40% if the FSW was deemed "attractive" by survey enumerators.

Of these studies, many do not explore the implications of findings on individual or public health, instead focusing on the concordance between data and theoretical economic models (e.g. monopolistic [43] or perfect competition [61], and whether models are correct in inferring a trade-off between sex work and marriage [53]). Despite high levels of methodological robustness, many studies miss the opportunity to focus on distal outcomes of epidemiological value, and are instead limited to intermediate outcomes such as risky behaviours or pricing.

By contrast, some studies use high-quality epidemiological data to estimate behaviours of clear public health importance. Two innovative studies explore the responsiveness of

the premium to epidemiological risk factors: Arunachalam and Shah[40] explore whether the condom differential is influenced more by intrinsic client preference for unprotected sex, or a 'true' compensating differential component which varies with the risk of STI or HIV acquisition. They find evidence that the latter drives the magnitude of the premium and estimate an 8% premium for unprotected vaginal sex, which increases substantially with the type of act and perceived risk of a client having an STI; unprotected anal sex with a risky client bears an additional 73% premium. Manda[62] estimates that 83% of the premium observed in Kenya can be explained by the sex-worker bearing the risk of pregnancy, with the remaining 27% attributable to STI risk. These studies demonstrate that FSWs in these contexts (Kenya, Ecuador and Mexico) have sufficient information and agency on epidemiological risk factors to rationally adapt pricing models according to risk, and that the supply of unprotected sex is likely both higher-priced and lower in quantity than low prevalence areas.

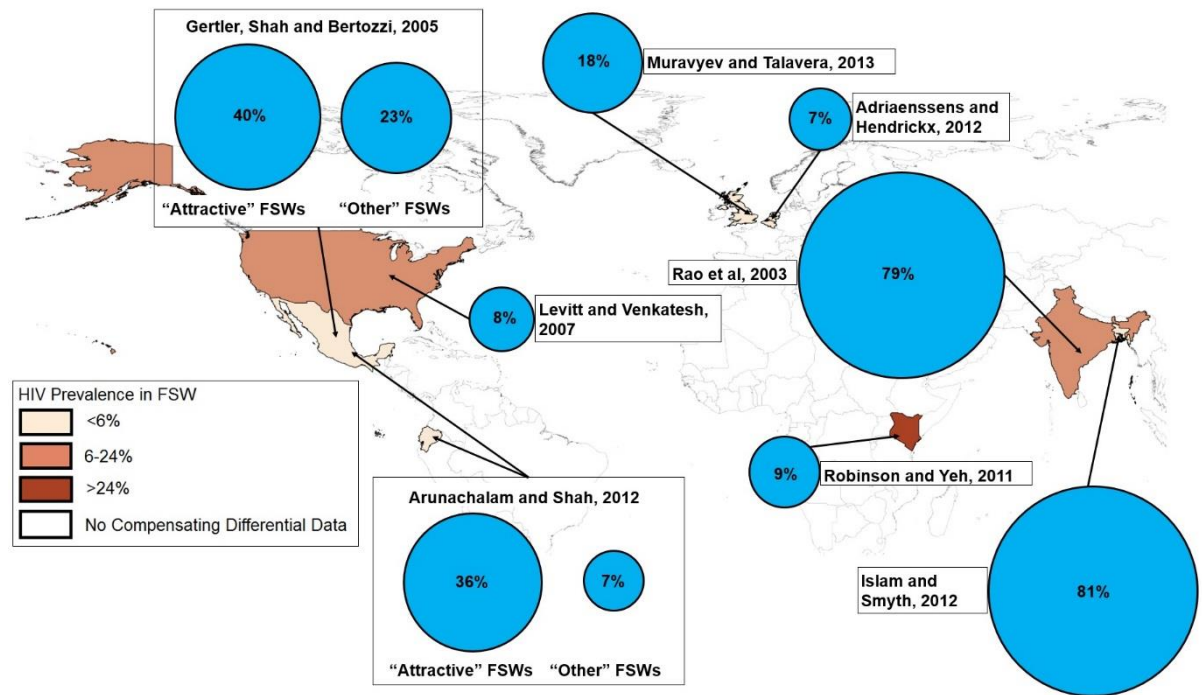
Among the largely methodologically robust literature, one paper stands out due to its estimation of a positive premium for protected intercourse after four years of a condom promotion campaign[65], yet its methodology is flawed.¹ All other identified studies which do not correct for endogeneity biases find a positive price premium for unprotected sex. For example, Elmes et al.[55] estimate that clients in Zimbabwe paid 43% more for unprotected sex, and Ntumbanzondo et al.[67] suggest that FSWs in Kinshasa charge up to 3.5 times more for unprotected intercourse. Since not adjusting for unobserved correlation between individual-level factors, which influence both condom use and price (e.g. by not accounting for unobservable elements of bargaining power), would bias estimates towards the zero, evidence of the existence of a condom differential is strengthened by findings of a significant premium in this literature. The

¹ The paper uses a three-stage least-squares method to account for the reverse-causality between price and condom use, a potential source of endogeneity. However, this method does not tackle other sources of possible endogeneity for example omitted variable bias

methodological approach of many of papers is strong, using econometric methods to account for potential biases in estimating the impact of condom use on price, either using FSW fixed-effects models or taking an instrumental variable approach. The results of studies that do this are summarised in Figure 3, which displays the considerable heterogeneity in estimates of the price premium for unprotected sex. The number of studies is too small to assess variation statistically, however visual examination indicates a smaller price premium in high-income countries (between 7 and 18% in Europe and the USA) compared to low- and middle-income countries (up to 81%, though results are comparable in Kenya and among subgroups of “attractive” FSWs in Central and South America. There is no apparent correlation between HIV prevalence and the price premium across studies, yet variation in sampling methods and subsequent selection of different FSW populations makes comparison across contexts difficult. As noted above, within-sample evidence supports variation in the price premium according to epidemiological risk.

Whilst earlier studies focused on proving the existence of a price premium for unprotected sex, as data and computational capacity have improved in recent years studies have begun to focus more intensively on heterogeneity in sex work, FSWs, and clients. Indeed, heterogeneity is a key theme emerging from the Oxford Handbook on the Economics of Prostitution. Cameron [41] explores the commercial sex market in North-West England, with a particular focus on heterogeneity in client preferences. He argues that the assumption made in much of the economic literature on sex work, that there is a single market with perfect competition, does not hold as economies of scope conditions have “failed to develop to satisfy the demand for variety” in this area. The marked increase sample sizes of recent studies, using novel datasets that were previously non-existent for example sex worker review websites[44, 48], will enable much more detailed analysis of heterogeneity within and across contexts.

Figure 3: Published econometric estimates of price premia for unprotected sex



Circle area is proportional to the price premium. FSW HIV Prevalence estimates are also included for – Bangladesh [82], Belgium [83], Ecuador [84], India [85], Kenya [86], Netherlands [83], Mexico [87], USA [88]. Constructed with GIS Shapefile [89] using ArcGIS Desktop 10 [90]. Empirical Papers: Rao et al. [3], Adriaenssens and Hendrickx[36, 91], Levitt and Venkatesh (2007), Arunachalam and Shah [40], Robinson and Yeh [33], Gertler, Shah and Bertozzi [14], Islam and Smyth [58], Muravyev and Talavera [66].

Further research demonstrates that heterogeneity in pricing for services exists systematically across and within cities[57]. Edlund and Korn find support for theoretical models predicting a relationship between age and marital status [53]. Sahni and Shankar[72] show that future work could be improved by explicitly incorporating heterogeneity when analysing sex work markets, in particular being aware of differences between FSWs who are readily available to participate in research and those who are not.

In general, the literature exploring individual- and act-level influences on FSW behaviour provides convincing evidence of a price premium for unprotected sex, found to be consistently present but varying in magnitude across context. Risks from HIV, other STIs, and pregnancy are shown to influence the magnitude of the price premium. In addition,

a number of studies note that considering heterogeneity is important to accurately reflect the complex dynamics of the commercial sex market. Edlund and Korn [53] find support for theoretical models predicting a relationship between age and marital status

Although this literature gives a comprehensive overview of individual- and act-level influences on FSW behaviours, the extent that these factors affect overall risk and economics choices, are also shaped by macro-level, systemic structures; these are discussed in the next section.

System-level factors

System level risks were defined as the 1) legality (or otherwise) of sex work in different contexts, 2) factors affecting the extensive margin, and 3) the structure of the sex work market.

Decriminalisation

Sex work differs in legality across countries, and while there has been a substantial push in recent years for decriminalisation, many laws remain restrictive[5]. 16 studies were found to examine how the legality of sex work varies across contexts, through theoretical [1, 4, 34, 35, 75, 77-81, 92] or empirical means [32, 41, 60, 61, 69].

Two empirical studies in high-quality journals indicate that legalisation of sex work led to a fall in rates of STIs in Mexico and Ecuador[32, 69]. However, the other empirical study presents indicative evidence that decriminalisation may increase total health risks: a natural experiment from the legalisation of indoor sex work in Rhode Island between 2003 and 2009[60] found evidence that the policy increased the number of transactions five years after implementation, which persisted after re-criminalisation. However, this study was not able to assess the impact of decriminalisation on the riskiness of sex acts supplied, for example through changes in condom use. Excepting this single empirical study, all literature supports the legalisation or decriminalisation of

sex work, in terms of predicting a reduction in the quantity of sex sold, or reducing the proportion of acts which are risky.

The lack of empirical data on decriminalisation has limited substantive empirical investigation. In its place, a theoretical literature – largely untested empirically – makes a number of predictions. Peppet[81] and Immordino and Russo[78][79] predict that legalising and taxing sex work would lead to lower levels of sex work than under optimal enforcement if made illegal, whereas regulation would minimise overall harms.

The theoretical literature would be greatly strengthened with further empirical examination. Two studies seek to explain the lack of examples of sex work decriminalisation, in part explaining why examples and data are so limited in number. Lee and Persson[80] demonstrate how policymaking is complicated when voluntary sex work exists alongside involuntary sex work, whilst Della Guista[35] argues that the continued illegality of sex work may be due to policymakers seeking to maintain the status quo to preserve reputations, even while the same model demonstrates clear benefits from deregulation to sex workers and wider society.

Factors affecting the extensive margin

Although a number of studies listed above analyse the *intensive margin* of how economic factors affect FSW behaviour within the commercial sex industry, nine studies seek to formally explain the *extensive margin* or entry into and exit from sex work[1, 4, 8, 39, 40, 46, 68, 74, 76]. This literature contains both theoretical and empirical contributions and, unlike the decriminalisation literature, all of the key theoretical contributions have been empirically tested for validity.

Edlund and Korn's seminal study[1] was the first to describe the relatively high rewards for sex work, despite a low training requirement. The authors suggest that FSWs trade-off capital they hold in the marriage market to become FSWs and that women who choose sex-work instead of marriage require sufficient compensation for this in the form

of greater wages. However, this theoretical model faces a challenge from empirical evidence as Arunachalam and Shah[39] show that FSWs were more likely to be married than not. Neither study explores the validity of this tradeoff across contexts with different social constructions of marriage.

A less critical inference of the model that a temporary increase in a male population would increase the propensity for women to choose sex-work over marriage was suggested to hold in a study by Cunningham and Kendall[46]. Finally, Peng [68] presents empirical evidence suggesting that the model's predictions hold in reality: 1) that the amount of sex bought and sold reduces with male and female income, and 2) that there is a wage differential for a sex worker over a woman with similar characteristics in the general population.

Cameron, in *The Economics of Sin*[4], presents a similar value-laden perspective of sex-work but gives a more sophisticated explanation for high FSW wages. The author cites reasons including risk, social exclusion and anti-social working hours, but does not empirically test the effect of these. Della Guista and colleagues describe an alternative (but not incompatible) model of sex-work to that of Edlund and Korn and argue that their framework “makes no restrictive assumptions regarding the gender, pay, and nature of forgone earning opportunities of prostitutes and clients”[76]. Instead, they explore the impact of reputational effects, suggesting that stigma plays an important role in determining the price and quantity of sex supplied. By construction, the model suggests that exogenous factors which decrease the probability of detection may increase the market for sex work. This hypothesis was later empirically tested by Cunningham and Kendall and found to be, to an extent, reflective of empirical evidence as street-based FSWs (who bear associated risks) moved to indoor working environments[44].

Willman's [74] approach models the commercial sex market from a different conceptual direction, however, presents similar findings. The paper uses a human capability approach to describe the *unfreedoms*, which FSWs face, on a daily basis from threats of disease and violence. The freedom to live a life free of disease and premature death is critical constituent part of the capability approach and is a key indicator in the United Nations Development Programme's Human Development Index[93, 94]. The key message from Willman's paper is, although many FSWs can command prices that include a sufficient monetary premium for risky acts, there is no reason to think that all FSWs have equal access to such premiums. In reality, depending on their location in the (segmented) labour market, FSW demand for compensation may be constrained by their mobility within the labour market resulting in differential compensation across segments. Thus, FSWs who have greater human capital and operate in more upscale market segments have fewer incentives to take risks; when these FSWs do take risks, they are compensated more generously than women are in other segments. Willman's model presents a more nuanced view than much of the literature on risk premiums, where a heterogeneous labour force offers a differentiated product to different clients. Although disproved to some extent by empirical work showing disease risk was more influential than segmentation of demand[40], this has implications for STI and HIV prevention programmes which should first target those FSWs most at risk from market forces to maximise benefit from limited resources.

Finally, Cunningham predicts that women who face lower variable costs of supplying commercial sex (for example reduced marriage market opportunities or social stigma) will enter into the market more frequently[8]. When applied empirically, the model indicates that women who faced larger fixed costs but decided to enter the market receive larger weekly earnings, however, they do not receive higher hourly wages.

In general, economic theory offers a restrictive view on decisions to enter the commercial sex market. In the models presented here, women *must* forgo other life opportunities, for example marriage [1], or perceive there to be sufficiently low levels of stigma around sex work[92]. In addition, women are assumed to act rationally and with agency, with the ability to accurately weigh up the individual risks and benefits of becoming a sex worker, fully predicting and accounting for social stigma and threats to health and wellbeing. Whilst there is some evidence that this may be the case in some contexts (e.g. Willman [74] shows that human capital is associated with agency), a large body of non-economic literature has shown that a wide range of micro- and macro-influences affect engagement in sex work. Many of these are not considered by the studies presented here, including, but not limited to, trafficking, poverty, family demands, partner coercion or violence [5, 95-98].

Market structure

Six studies explore how the structure of the market for commercial sex can affect FSW behaviours, with research largely focusing on how the presence of intermediaries (e.g. pimps/madams) interacts with FSW agency and ability to make healthy and rational choices. [44, 48, 52, 61, 77, 81]

For example, Li et al.[61] demonstrate that FSWs in Singapore have a high degree of agency in the absence of intermediaries and are able to discriminate between clients, despite substantial competition in supply. Similarly, Farmer and Horowitz[77] suggest that the presence of pimps in sex work markets dictates how much consumer surplus is present, but does not diminish supplier surplus (i.e. it will only affect client welfare if pimps are present). These two studies are in contrast with much of the empirical social epidemiology literature which suggests pimps can be symptomatic of exploitative sex work arrangements (e.g.[2, 99-101]).

Advances in technology, in particular the influence of the internet on increasing safety and information exchange in sex work markets, is tackled by Cunningham[44] and Peppet[81] who suggest that the internet has encouraged FSWs to move from recruiting clients from the street (an often unsafe working environment which can generate substantial negative externalities) to the virtual space where FSWs reportedly have more agency and influence over protection and risk behaviours. Thus, the rise of online solicitation has replaced a good deal of streetwalking, yet this augmentation of the commercial sex market appears to have only occurred among some age groups of FSWs in high-income countries. Furthermore, FSWs who have moved from on-street to virtual recruitment appear to mostly “carry” risky behaviours with them, potentially creating new disease risks in the (previously relatively safe) indoor-sector. In addition, Cunningham and Kendall [48] describe how internet-based soliciting makes previously unenforceable contracts between clients and FSWs enforceable, as online systems of client reviews act as a form of reputation mechanism, improving information exchange and increasing the implications of breaching agreements.

Taking a different approach, Ebenstein and Sharygin [52] estimate how demographic trends in China, in particular an increasing adult population sex ratio (a larger number of men compared to women), will impact the structure of the market for commercial sex. Although the authors predict that competition in the marriage market will lead to an increase in demand for commercial sex, particularly in rural areas, they do not link this data with epidemiological risk variation (e.g. HIV/STI prevalence), or explore how technology or the role of intermediaries might interact with risk.

This small but burgeoning literature on how the internet and mobile technology is changing the market for commercial sex is an example of the strength of using formal economic models to describe complex market interactions. In particular, the role of agency and information – both previously controlled by intermediaries between FSWs

and clients – are changing with the advent of review websites, which facilitate contact and information exchange between FSWs and clients. These structural changes to the market are beginning to substantively change the extensive and intensive margin of the commercial sex industry across contexts. Future research to understand how these changes affect the risks FSWs face, and choices they make, will be critical to understand and minimise risks to FSW and client health. There is a clear need to update models and assumptions made in literature published before the advent of internet-based solicitation, and renewed focus on information and agency will likely offer important insights.

Exogenous factors

Seven papers considered the impact of exogenous economic factors on the market for commercial sex [33, 37, 46, 50-52, 70]. Three of these explore the response of women to exogenous income or health shocks (which themselves require large expenditure), specifically measuring their impact on engagement with sex work and the mix of services provided. Robinson and Yeh[33] find that FSWs in Kenya, on days when a household member falls ill, or when she recovers from an STI (argued to be exogenous by the authors), women are much more likely to see a client and provide riskier services such as unprotected or anal sex. In a different paper analysing the same sample, Robinson and Yeh[70] find that women use regular clients as a financial safety-net, where men “act like husbands” to provide money for rent, school fees or funeral expenses. When FSWs fall ill, regular clients contribute around 25% of the income shortfall from time lost working and contribute substantially to funeral costs. Similarly, de Walque et al.[50] find that food insecurity causes women who do not usually sell sex to enter the market, though do not investigate the impact on services supplied by full-time FSWs.

Finally, events in the political world have been shown to impact the market for commercial sex through two routes. Firstly, Cunningham and Kendall[46] reinforce

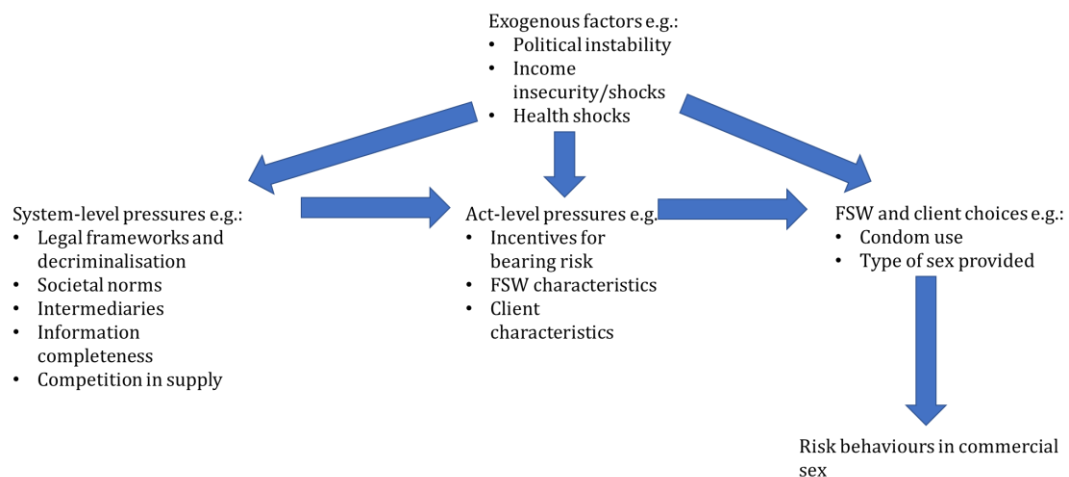
previously mentioned literature around the flexibility of the supply-side of the market. They use a natural experiment of political conventions in the US to show that the supply of commercial sex is responsive to demand – convention presence led to a more than 40% increase in adverts for sex work on classified advertisement websites. Secondly, Dupas and Robinson[51] show that two months of political instability after national elections in Kenya in 2007, led to large reductions in income, expenditure and consumption. Unable to access “adequate insurance or consumption smoothing devices” to manage income losses, more FSWs provided more, riskier sex than before the crisis. de Araujo[37] also shows that stability, political and economic, affects the amount and type of sex sold in commercial markets. Finally, Ebenstein and Sharygin[52] show that migration for economic reasons, a male-weights sex ratio, and observed willingness of married FSWs to provide unprotected sex have the potential to increase HIV and STI incidence.

Though this section of the literature is small, it is clear that exogenous factors can substantively impact the commercial sex market and, notably from a public health perspective, affect risky behaviours alongside economic pricing and supply factors. There are an almost infinite number of potential exogenous factors that may affect, positively or negatively, the choices of FSWs and clients; it is impossible to have a coherent public health response to all. Yet some, for example elections or public holidays, may be more predictable than others, and interventions could be designed to address predictable shocks to the commercial sex market. Increasing the availability of credit, or providing of cash transfers to aid earnings and consumption smoothing, may be one such approach to reduce short-term financial vulnerability and subsequent provision of more lucrative risky acts. More research is needed into the mechanisms underlying behavioural responses to exogenous events to identify vulnerability-reducing solutions.

Conceptual framework

Figure 4 displays the conceptual framework derived through this review. Risk behaviours of clients and FSWs are influenced by factors in the three categories used to synthesise studies. Act-level factors are the most proximal to choices and include FSW and client characteristics (including differential bargaining power between parties), alongside the influence of financial incentives to bear risk. System-level factors influence choices indirectly by shaping act-level factors and include legal frameworks (which can restrict the ability of FSWs to work in safer indoor environments), the presence of intermediaries such as pimps or madams and subsequent reductions in agency, and the extent to which competition from other providers may influence bargaining power. Finally, exogenous factors can impact choices directly, such as through increasing the amount of unprotected sex a FSW provides after an income shock, or through influencing broader pressures of such as increased competition from new entrants to the market.

Figure 4: Conceptual framework to explore choices and behaviours in commercial sex



Discussion

Overview of literature

This paper comprehensively reviews the literature on the influence of economic factors on the choices of FSWs. 56 papers were identified, many of which included some empirical work. The largest body of the literature sought to estimate the effect of various FSW, client, or act characteristics on price – particularly seeking to identify the *condom differential*, the price premium for unprotected sex, which was estimated to be between 9% and 81% in different contexts. The second largest body of work analyses or simulates the effect of legalising (or decriminalising) sex work on the number of women engaged in the industry, and the number and type of acts supplied. A body of conceptual and largely theoretical studies modelled FSW decisions to engage in the commercial sex industry at all (the extensive margin). Finally, a small number of papers examined the effect of seemingly unrelated events on the market for commercial sex. These papers particularly highlighted the fragile economic circumstances of those on the periphery of the commercial sex market, and the potential unmeasured consequences of exogenous shocks on the quantity and type of sex sold.

Strengths of literature

This review identified a large number of methodologically robust and theoretically coherent contributions to the economics of sex work. A strength of basing empirical analyses on formal economic theory is theoretical validity across settings, as shown by the multitude of empirical work using similar theoretical models in estimating a compensating differential for condom use. Even where models differ structurally, such as predicting the impact of sex work decriminalisation, common predictions of positive outcomes from decriminalisation, including lower rates of STI and HIV transmission and improved FSW security, provide greater validity as a whole body of evidence than the sum of parts.

Furthermore, many elements of the economic literature identified here are consistent with wider sociological and epidemiological work around factors on FSWs. Individual studies focus on one or two narrow areas of research. However, economic work covers a very wide range of issues affecting FSWs and their choices. This is exemplified by economic work tackling every structural determinant identified in Shannon et al.[5], many of which combine to affect HIV/STI acquisition and transmission dynamics among FSWs.

Limitations of literature

No study was found to consider the impact that new HIV prevention products might have on the choices and behaviours of FSWs. In fact, the only method of HIV or STI prevention considered by the economic literature to date is condoms despite a number of trials and demonstration projects for PrEP in recent years. Although consistent condom use is encouraged to continue during PrEP use[102], there is a concern that condom use will be reduced due to diminished risks of unprotected sex alongside incentives to use condoms for protection[103]. There is a need for the economic literature to engage with outstanding questions around the potential impact of PrEP on FSWs and clients.

Many of the theoretical and empirical models in this paper make assumptions around the agency of FSWs, particularly the structural literature which assumes that women a) can adjust their supply of commercial sex acts according to demand, b) that they are empowered agents who (albeit with sometimes lower bargaining power than clients) are able to opt-out of providing risky, or any, commercial acts, and c) that FSWs are a broadly homogeneous group either within studies, across studies, or both. These assumptions may not hold for a number of reasons.

Firstly, FSWs may not be able to adjust their supply of commercial acts if an intermediary is forcibly making women work. Although trafficking forms a large part of the policy discourse around sex work, other evidence shows that the majority of women engaged

in the sex industry, particularly in higher income countries, have not been trafficked[104]. Nevertheless, little attention is paid in this literature to the possibility that exploitation could be occurring, nor its potential impact. Furthermore, exploitative arrangements are not considered as a potential outcome of models of legalising sex work. Although not considered a significant negative outcome of legalisation, trafficking and exploitation should be considered and monitored as possible unintended outcomes.

Secondly, the ability of a FSW to opt-out of providing any commercial act at all depends on a range of factors, including the physical location where she meets clients and the potential for violence and abuse, alongside the wider financial situation she and her family faces. Evidence from India has shown that enhancing the social cohesion of FSWs as part of a HIV prevention programme improved the programme and empowered women to refuse services to bad clients[105, 106]. Nonetheless, street-based FSWs face a considerably riskier working environment than their indoor-based peers, are more likely to suffer from violence from clients of police, and are less likely to participate in community-led programmes. Economic and epidemiological literatures also disagree on the impact of intermediaries in sex work; studies in this review imply that intermediaries are value-adding, whilst epidemiological studies conclude the opposite[2, 99-101]. More research is needed to explore this nuanced relationship.

Third, although later literature (e.g. [72]) argues for a greater consideration of heterogeneity within and across studies, the majority of the literature focuses on eliciting whole-sample averages. FSWs are a highly heterogeneous group; studies characterise populations by age, country of work, workplace, ethnic background, or experience in the industry – for example – but there is no generalisable taxonomy of sex work, nor will the risks of working on the street compared to indoors be comparatively similar across countries. Economic models seek to do exactly this and describe sex work in a formally defined, generalisable manner. This may be, in part, due to the traditional

use of empirical data to prove overarching economic theories, however, does not suit the huge variation in sex work contexts. More focus could be placed on the heterogeneity across different sex work contexts, including the agency of FSWs compared to clients, their negotiation power and ability, and the market power they hold relative to other FSWs.

Finally, none of the literature identified literature satisfactorily explores the nature of the complex, two-way relationship between condom use and price. Isolating the effect of condom use on price is an interesting economic question, but the estimating effect of price changes on condom use would provide important data for programmes seeking to increase the economic empowerment of FSWs. For example, a Mexican programme gave male sex workers cash transfers conditional on remaining STI free, a proxy outcome for consistent condom use[107].

Strengths and limitations of review

This study is the first to comprehensively review the literature assessing how the choices and behaviours of FSW may be impacted by economic factors. It used a systematic search strategy to identify potentially relevant papers, and provides a comprehensive overview of the research that has been conducted on the economics of sex work.

Although the review identified a large body of work, the range of topics potentially relevant to the research question, alongside the variation in terminology used to describe aspects of studies, may mean that potentially relevant studies were omitted. Although the risk of omission was reduced through snowballing and screening lists of studies which cited included studies, we cannot guarantee that all relevant studies were included. For example, authors of epidemiological studies or those published in biomedical journals may not use the explicitly economic terminology of the search strategy, nor necessarily cite papers from economic journals. This may mean results are biased against the inclusion of epidemiological or biomedical research.

Conclusion

This comprehensive review synthesises the results of 44 studies exploring a range of macro- and micro-level factors on the choices of FSWs. Identified studies were found to fit into three broad categories: act- and individual-level factors, system-level factors, and exogenous factors. The generalisability of economic models offers advantages, and the wide range of economic work carried out on commercial sex work is consistent with public health and epidemiological findings. However, no studies explore the potential impact of new HIV prevention products, while included studies require assumptions around FSW agency which may not hold in all contexts.

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Implications for thesis

This thesis has the opportunity to contribute substantively to the literature by exploring the impact of new HIV prevention products on the choices of FSWs. PrEP use may inhibit condom use directly where FSWs substitute away from condoms due to intrinsic preferences against their use. However, where a price premium exists for condomless sex as shown in many contexts, the additional monetary incentive may lead to an additional risk compensation, through a reduction in condom use or increase in commercial sexual activity. Also, client preferences may also change after the introduction of PrEP if they infer a lower risk from demanding unprotected intercourse, increasing their willingness to pay for unprotected sex.

Papers R3 and R4 seek to explore if these scenarios might happen and if they could matter. The results of this review were used to refine the scope of the FSW DCE, and contribute to the long-list of potential attributes which were after refined during pre-piloting and testing.

Chapter 4: How well do discrete choice experiments predict health choices? A systematic review and meta-analysis of external validity

Overview of paper

Because DCEs can be used to assess preferences for products or services which do not yet exist, they are frequently used to predict end-user uptake. However, DCE predictions are sometimes perceived as inaccurate, largely due to hypothetical bias where respondents are not faced with a choice in reality. For DCEs to be effectively used to predict real world behaviours – as they are employed in this thesis – it is important to quantify the extent to which they may give misleading results.

This research paper systematically reviews the health literature for studies comparing DCE predictions to observed choices made by individuals and uses meta-analytic methods to synthesise estimates of the predictive ability of DCEs. This paper meets the methodological objective 6, to assess the reliability of DCEs to predict health-related choices. It has been revised and resubmitted to the *European Journal of Health Economics*.

This chapter provides evidence on the validity of using DCEs to parameterise uptake and risk compensation parameters in models, as applied in results papers R2 and R4. It also meets research objective 6, which will be described in the next chapter, to assess the reliability of DCEs to predict health-related choices.



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Student	Matthew Quaife
Principal Supervisor	Fern Terris-Prestholt
Thesis Title	Using stated preferences to estimate the impact of new HIV prevention products in South Africa

If the Research Paper has previously been published please complete Section B, if not please move to Section C

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Stage of publication	Revised and resubmitted

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How well do discrete choice experiments predict health choices? A systematic review and meta-analysis of external validity

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Abstract

Discrete choice experiments (DCEs) are economic tools which elicit the stated preferences of respondents. Because of their increasing importance in informing the design of health products and services, it is critical to understand the extent to which DCEs give reliable predictions outside of the experimental context. We systematically reviewed the literature published DCE studies comparing predictions to choices made in reality; we extracted individual-level data to estimate a bivariate mixed effects model of pooled sensitivity and specificity. Eight studies met the inclusion criteria, and six of these gave sufficient data for inclusion in a meta-analysis. Pooled sensitivity and specificity estimates were 88% (95%CI: 81%, 92%) and 34% (95%CI: 23%, 46%) respectively, and the area under the SROC curve (AUC) was 0.60 (95%CI: 0.55, 0.64). Results indicate that DCEs can produce reasonable predictions of health-related behaviours. There is a great need for future research on the external validity of DCEs, particularly empirical studies assessing predicted and revealed preferences of a representative sample of participants.

Introduction

Discrete choice experiments (DCEs) ask participants to make choices between hypothetical alternatives, using choice modelling methods to analyse data. They are attractive tools for research and policy as they offer a flexible methodology to estimate which attributes are important in decision making. Participants are asked to choose their preferred of, generally, between two and five alternatives over a number of choice tasks (usually around ten). Data are analysed using discrete choice models [1], the results of which can be used to determine the relative importance of different attributes to respondent choices. Results can also be used to predict demand, termed as market shares in the marketing literature[2]. DCEs are being increasingly used in health to study patient and/or physician preferences in academic studies, health technology assessments, and regulatory risk-benefit assessment [3, 4]. Particularly useful is the ability to include products or attributes in DCEs which do not exist in reality, and for which no observational or trial data exist [5].

In recent years, DCEs have proven increasingly popular in the health domain, whilst a large (mostly non-health) economic literature has developed around the design, analysis and application of DCEs [2, 6, 7]. Yet DCEs ask respondents to make hypothetical choices, and it is important to ensure that they measure what researchers think that they do. Disparities between revealed and stated preference data are, in part, due to the hypothetical nature of DCE tasks; this divergence is termed *hypothetical bias*. There has been no widely accepted theory to explain hypothetical bias which, following Beck et al. [8], we define in this paper as discrepancies between preferences exhibited in DCEs to those exhibited in reality. Hypothetical bias may originate when choice tasks do not fully reflect reality in the nature or characteristics of choices, when respondents have incomplete preferences, or if respondents perceive a vested interest in over- or understating the importance of particular attributes.

Where the true attributes of a good or service are known, predicted probability analysis (PPA) uses DCE results to predict utility-maximising choices. Under the assumption that individuals are rational, DCEs can approximate which choice people would make given the option in reality [9, 10]. PPA is common outside of health and is increasingly being applied by health economists to predict demand for a range of health-related choices, including HIV prevention products [11], contraceptive services [12], vaccination [13] and migraine treatments [9].

In the early stages of introducing health products or services, there is often a great deal of uncertainty around their potential impact and subsequent cost-effectiveness. DCE predictions can be particularly useful for estimating the uptake of new products or services where observational data, from trials or pilot projects, are not available [12, 13]. In the absence of observational data, for example in from a pragmatic trial or demonstration project, “expert opinion” is often used to generate uptake predictions which are then commonly used to inform impact or cost-effectiveness models [14]. In a previous paper, the authors of this study suggest that DCEs can provide a useful empirical alternative to expert opinion, whilst also offering additional benefit through accounting for synergistic relationships between different product and service attributes and use, which are commonly ignored[15].

Background on validity in DCEs

In health, around 60% of studies include internal theoretical validity checks, whilst non-satiation and transitivity tests are applied less frequently[3]. A recent study demonstrated that, of the 112 health DCEs published in 2015, 49% included at least one internal validity check, yet there were substantial differences in how researchers dealt with indications of poor validity i.e. 46% of studies using a dominance test excluded respondents who failed the test[18].

By contrast, *external validity* is concerned with ensuring the comparability of hypothetical and actual choices. Because respondents are not obliged in reality to make the choices they indicate in a DCE, hypothetical bias may reduce the usefulness of DCE results [19, 20]. There have been some substantive contributions to the methodological literature on the external validity of DCEs (e.g. [16, 21-23]), yet much of the focus in the literature has been on maximising the internal validity of DCEs. Whilst this is important, there has been very little empirical work assessing whether choices made in DCEs in fact reflect those made in reality, or the circumstances in which they may offer more or less reliable inference[16].

This paper considers variations in external validity in health DCEs attributable to hypothetical bias, and is the first systematic review and meta-analysis assessing the ability of DCEs to predict health behaviours. Proving external validity is important to the practical application and use of DCEs, yet despite their growing popularity there has been little research on their external validity in the health domain [22, 23].

There are many reasons why hypothetical bias may exist, including that people may be fundamentally rational but inconsistent in utility maximisation, e.g. when they are paying more or less attention to a decision context. Indeed, the choice architecture surrounding real-world and hypothetical choices has been shown to affect choices, including healthy eating, physical activity, and alcohol use[24-26]. Furthermore, if DCEs are not incentive compatible, respondents may try and answer strategically, for example to understate their willingness to pay for public services[27, 28]. Behavioural economic research challenges the theory that we are all variants of *homo economicus*, but there has been limited work exploring if behavioural heuristics influence preferences to a greater or lesser extent in stated preference tasks than in reality [29, 30]. Additional reasons why differences may exist in health fields include: difficulties in acquiring revealed preference data due to failures in healthcare markets; the lack of a market analogue for

many health decisions; or vested interests from researchers not wanting to reveal the ability (or lack thereof) of DCE models to accurately predict choices and behaviour [21, 23, 31, 32].

We note that literature exists, mostly outside of a health context, evaluating the external validity of WTP estimates from stated preference exercises. These exercises are different from DCEs whereby, instead of participants choosing between a set of alternatives, people are presented with open-ended questions, for example how much they would be willing to pay to avoid a certain occurrence. The external validity of WTP estimates has been explored fully and recently in the literature, and we therefore do not include WTP studies in this review. This work explores the external validity of willingness-to-pay estimates from contingent valuations and conjoint analyses, mostly in transport fields [33-35], including three meta-analyses [36-38]. These studies conclude that hypothetical bias can be substantial, with median bias levels ranging from 25% to 300%. Furthermore, efforts to reduce hypothetical bias through a number of methods, such as increasing consequentiality of choices or “cheap-talk” strategies, have also been shown to have mixed results [26, 39-41].

Rationale for review and aim

There has been no synthesis of the predictive abilities of DCEs in health, despite a substantive and recent increase in the number of studies using estimated choice probabilities from DCEs to predict choices, e.g. [9, 42]. These studies implicitly assume that DCEs have sufficient external validity to provide meaningful results. More generally, there has been no systematic review of studies exploring the external validity of any stated preference tasks in health. Existing reviews focus on summarising DCE applications [3, 7, 43], collating preference research on particular health or disease areas [44, 45], or synthesising methodological innovations to maximise internal validity [46].

This review aims to systematically review studies comparing stated preference choices, as modelled through predicted probability models resultant from DCE data, to revealed preference choices as gathered through observational or survey means. We report published evidence, describe the quality of included studies using an adapted quality checklist, and quantitatively synthesise the predictive ability of DCEs.

This review is the first to systematically evaluate and synthesise studies which observe participants' stated and revealed preferences through comparing DCE data to real-life health choices. Its findings will enable researchers and policymakers to assess how useful DCEs might be in predicting individual choices..

Methods

Search strategy

We searched the following databases to ensure a comprehensive exploration of the health, economic and decision science literature: 1) PubMed/Medline; 2) EMBASE; 3) CINAHL; 4) Econlit; 5) Social Policy and Practice; 6) Science Direct. An iterative strategy was employed and the references of identified articles examined by hand for further relevant material. The search included all available years up to August 2015. The following keywords (alongside relevant MeSH terms where databases permitted) were used to build the search strategy:

- Discrete choice experiments (“discrete choice* OR choice experiment* OR stated preference* OR DCE OR conjoint analysis”)
- AND
- External validity (“external validity OR predict* OR hypothetical bias* OR market share* OR revealed preference*”)

Inclusion and exclusion criteria

We included studies using a discrete choice experiment methodology to predict health-related choices and compared these predictions with observed choices in real-life. Studies were not excluded by population or the nature of choice tasks presented to participants. Studies obtaining revealed preference data from lab-based studies were excluded as these may be subject to similar concerns over external validity as DCEs themselves. The term conjoint analysis was explicitly included in the search strategy, and studies incorrectly labelled as conjoint analyses, when they were in fact DCEs, included in the screening process. We excluded:

1. Studies using a preference elicitation method other than a discrete choice experiment (for example, contingent valuation or conjoint analyses);
2. Studies using “lab-based” experiments to elicit revealed preferences;
3. Letters, general commentaries or perspectives;
4. Studies without English language titles or abstracts.

Screening of Studies for Eligibility

We imported all identified references into reference management software[47] and removed duplicates. First, titles and abstracts were screened by one researcher and irrelevant articles excluded. Secondly, the full text of selected papers was screened independently by two researchers against the eligibility criteria. Any disagreements were resolved by discussion. Records of studies were kept as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist [48]. Data were then extracted into a predefined extraction form. Where information was lacking, attempts were made to contact corresponding authors to obtain the maximum quantity of data.

Assessment of Study Quality

The characteristics of included studies were assessed by two reviewers against a tool of 17 criteria based on that of Mandeville et al. [43] which is itself an adaptation of the “good-practice” checklist of Lancsar and Louviere [49]. The quality criteria tool used is presented in *supplementary material S1*. We remove the criteria of using an efficient design, since this may not be an indicator of study quality, and the criteria of ensuring a sufficient response rate due to the subjectivity of what may be considered *sufficient*. In addition, we amend the criteria that attribute and level choice should be “grounded in *qualitative* work with the target population”, to “grounded in *piloting* work with the target population”. Mandeville et al.’s method only assesses criteria which may substantively affect the quality of included studies, thereby avoiding common criticisms of quality checklists that they are poorly correlated with study validity and measure the quality of reporting rather than that of the underlying study [50].

The checklist of Lancsar and Louviere does not consider external validity, except through the broad question “Was internal or external validity investigated?”. Therefore, we drop this criterion in favour of five further criteria to assess the reliability of external validity assessment. We based four of these criteria on Lancsar and Swait [51] who specify some testable reasons that stated preference models might fail to be externally valid. Finally, we note the potential for selection bias in studies where observational data were gathered on a non-random subset of DCE participants and include an additional criterion to ensure that we account for potential selection bias in comparisons between predicted and actual choices. Both reviewers independently evaluated the quality of included studies by assessing whether the criterion for each study was met or not. If the information available for a criterion was insufficient to evaluate its achievement, we noted this as a separate category.

Statistical Analysis

Because DCE predictions are a form of binary classification test, to synthesise the outcomes of included studies we employ the array of methods used in assessing clinical diagnostic tests. In the context of DCE predictions, high sensitivity (true positive rate) would indicate reliability in predicting opting-in behaviours. We define an opting-in behaviour as a choice, in the DCE or a real-world context, to use a product or service that a respondent does not currently use. . High specificity (true negative rate) would indicate reliability in predicting opting-out behaviours, which we define as a respondent choosing not to use a product or service in the DCE or real-world context.

Synthesising sensitivity and specificity estimates requires more sophistication than other quantitative syntheses, due to between-study heterogeneity, and the correlation between sensitivity and specificity estimates. When differences between studies are thought to be only due to sampling variation, it would be appropriate to pool estimates though sample size weighted averages of sensitivity and specificity. However, it is likely that variability beyond chance can be attributed to between study differences (e.g. study design, method of data collection, context, interviewer or self-administration). Due to the range of DCE methods and study contexts, we use a random effects model to attempt to account for explainable and unexplainable heterogeneity [52].

There is likely to be interdependence between sensitivity and specificity measures which requires specific consideration in meta-analytic models [53]. To account for this, we use bivariate mixed-effects logistic regression through the *midas* command in STATA 14, which assumes independent binomial distributions for true positives and negatives conditional on the sensitivity and specificity in each study [54, 55]. By jointly modelling sensitivity and specificity, this method preserves the bivariate data structure of the data and is an improvement on the standard analysis method of applying the DerSimonian and Laird random effects model [52]. The potential for publication bias was assessed

through Egger's test[56]. No test for publication bias is without methodological issue[57], yet Egger's test for funnel plot asymmetry is recommended for use by PRISMA guidelines[58].

Finally, we conduct bivariate multivariable meta-regression to explore heterogeneity by regressing sensitivity and specificity estimates on five study-level characteristics: mode of DCE administration (paper/computer), whether the DCE is related to a prevention or treatment choice, the number of DCE choice sets, the number of alternatives within a choice set, and the percentage of DCE respondents for whom revealed preference data were analysed. The effect of each covariate on sensitivity and specificity is estimated separately[54].

Results

Figure 1 details the flow of papers through the study. In total, 6,383 studies were identified through database searching and one additional study identified through its presentation at a health economics conference. The full text of 13 articles was reviewed for eligibility, eight were considered for a qualitative synthesis, and six included sufficient quantitative information for inclusion in a meta-analysis. Figure 2 shows publications identified by year.

Notably, there were very few studies which directly assessed the external validity of DCE predictions. Of the studies that have been published (two were found in pre-publication, conference abstract stage, one of which was published whilst this study was under review[59]), 5 (63%) were published since 2015, suggesting that the external validity of DCEs is receiving more attention than in the past. Seven studies (88%) sought to predict the choices of patients over a broad range of health choices, from vaccination to sexually-transmitted infection testing to prospective mother's choice of birth location. One study sought to predict the choices of healthcare professionals as they appraised new

medicines. Six studies (75%) presented information at the individual level and are included in the meta-analysis.

Assessment of quality of included studies

Results from the quality assessment of included studies are presented in *supplementary material S2*. Overall, the quality of studies was high; the design and implementation of DCEs were often of good quality. However, the additional criteria we add to explore the robustness of study external validity indicate some notable weaknesses.

When assessed by criteria outside of those exploring external validity, the included studies were of high quality. For example, most DCEs were piloted in a relevant target population and allowed participants to “opt-out” of making a choice. However, included studies may be subject to selection bias. The response rate of the DCE task was often low, while data on actual behaviour was not gathered for the full sample of people who completed the DCE. If participants who did not complete the DCE, or who did and were not followed-up, are non-randomly different from those who were included in final analyses, systematic bias would be introduced into results. If participants were more likely to be included in follow-up when they opted-in to a choice, this would overstate the predictive ability of DCEs.

We note that two studies meeting the inclusion criteria, Mohammadi et al. [60] and Chua et al. [61], were identified in conference abstract form. Although the former was published as a full paper during the review process of this study[59], the latter was not and does not include sufficient information to assess against all quality criteria.

Figure 1: PRISMA diagram of review process

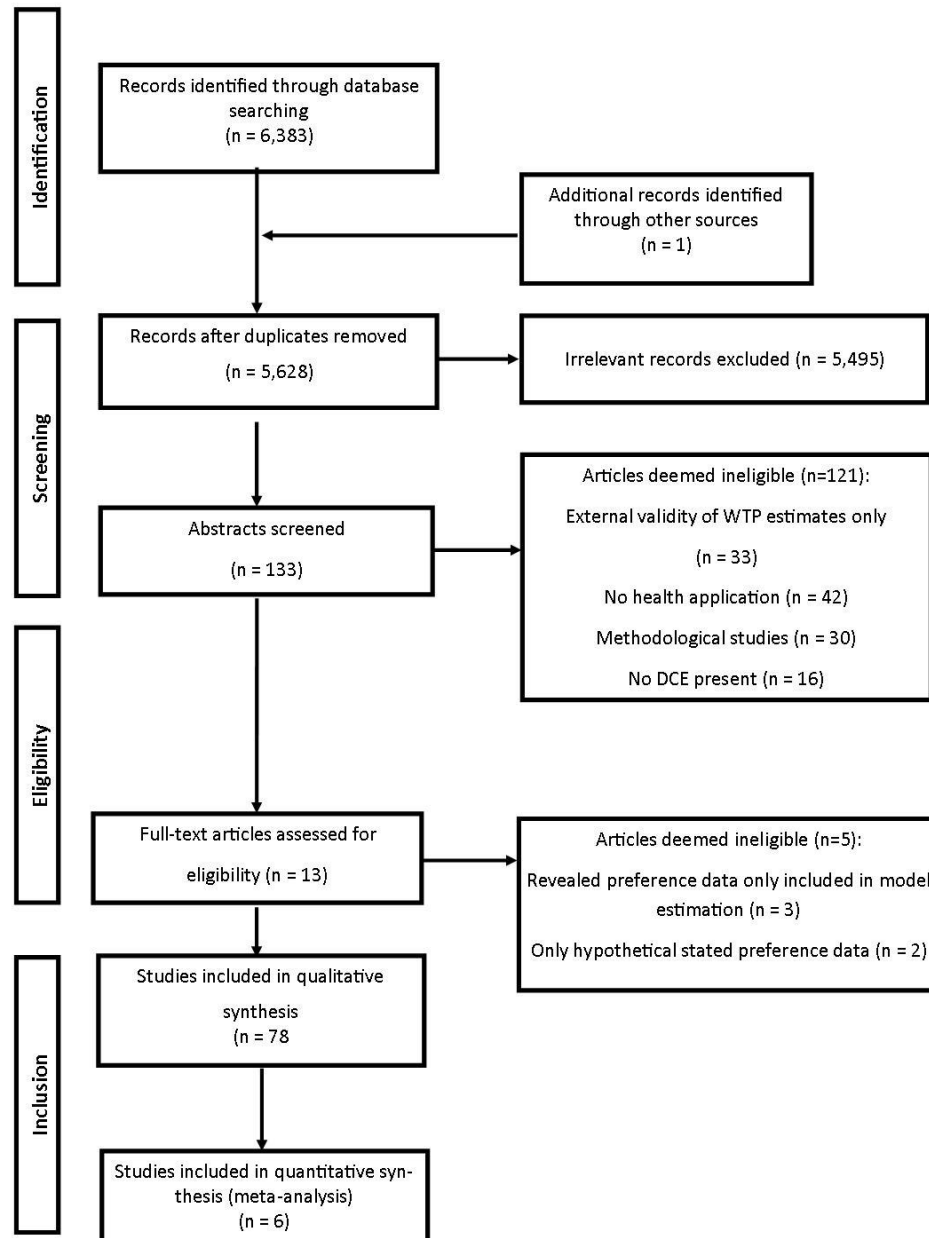
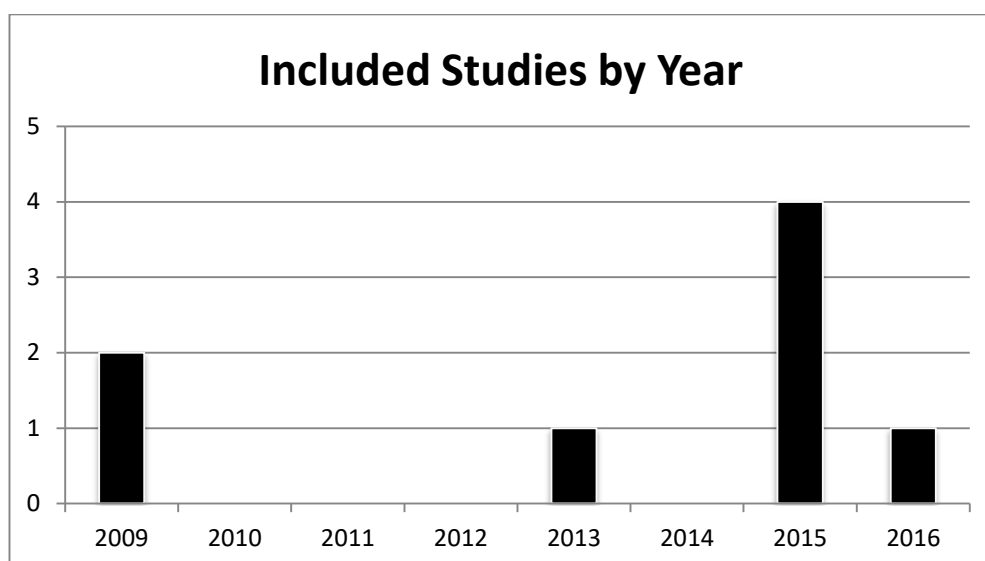


Figure 2: Summary of publication date of included studies



Quantitative synthesis

Table 1 presents information on all included studies, while table 2 displays the data extracted to assess the predictive ability of DCEs. We consider 844 observations where opt-in or opt-out choices were correctly predicted 75% of the time; 65% of incorrect predictions were false positives. Figure 3 displays the sensitivity and specificity estimates for each study². These estimates were calculated from the raw data.

In this context, DCEs predict that an individual will either make or not make a particular choice in reality. Therefore, a higher sensitivity would indicate that DCEs are good at predicting when individuals would choose reality, while a higher specificity would indicate that DCEs reliably predict that individuals will not make a particular choice.

We use a bivariate random-effects model to account for substantive heterogeneity between studies, and produce pooled estimates of sensitivity and specificity. Pooled estimation suggests that the sensitivity of DCE predictions was relatively high (0.88 95% CI: 0.81, 0.92), whilst specificity was substantially lower (0.34, 95% CI: 0.23, 0.46). These

² One study (Krucien et al.) predicts the uptake of two treatments, and we present each separately in this analysis

results suggest that DCEs can be moderately informative for predicting future behaviour. Specifically, when DCE data suggest that somebody *will* behave in a certain way (for example, opting for a treatment or programme), this is a more reliable statement than when DCEs suggest somebody *will not* behave in a certain way (for example, they will not use a treatment or programme). There is no consistent pattern of the number of false positives outweighing the number of false negatives, however it is possible that imperfect sensitivity may result in DCEs over-predicting demand. For the remainder of this paper, we will use the term "opt-in" to denote those participants who the DCE predicts would use a product or service.

As sensitivity and specificity estimates are pooled through bivariate random effects modelling, we expect the two estimates to be interdependent. *Supplementary material S3* shows a bivariate box plot which describes the extent to which sensitivity and specificity are interdependent with the inner oval representing the median distribution of estimates, and the outer oval the 95% confidence bound. These results indicate that there was a degree of heterogeneity between included studies, as three reside outside of the median distribution while one study tends towards being defined an outlier. There was no strong indication of a skew towards sensitivity or specificity. According to Egger's test there was no evidence of publication bias ($p=0.56$), however the capacity for this test to detect publication bias from a limited number of small studies is limited [56].

Table 1: Characteristics of included studies

No.	Authors	Publication Year	Title and Journal	Place of DCE Deployment	Sample Size*	Survey Mode	Study objective
1	Krucien et al. [62]	2015	Empirical Testing of the External Validity of a Discrete Choice Experiment to Determine Preferred Treatment Option: The Case of Sleep Apnea, Health Economics	Patient group in a French hospital's sleep unit	SP: 140, RP: 138 (99% follow-up)	Face-to-face interview with trained nurse	To explore patient preferences for alternative treatments for obstructive sleep apnea syndrome (OSAS)
2	Lambooi et al. [63]	2015	Consistency between stated and revealed preferences: a discrete choice experiment and a behavioural experiment on vaccination behaviour compared, BMC Research Methodology	Parents with child <2 weeks old in The Netherlands	SP: 906, RP:247 (27% follow-up)	Paper-based questionnaires, medical records	To compare vaccination scenarios against hepatitis B among the parents of newborn children
3	Mohammadi et al. [59]	2015	Testing the External Validity of a Discrete Choice Experiment Method: An Application to Latent Tuberculosis Infection Treatment, Value in Health.	Patients diagnosed with latent TB infection attending TB clinics in British Columbia, Canada	SP: 214, RP: 204 (95% follow-up)	Not reported in abstract	To explore patient preferences for latent TB treatment, and predict uptake
4	Salampessy et al. [64]	2015	The Predictive Value of Discrete Choice Experiments in Public Health: An Exploratory Application, Patient	Patient group in Utrecht, The Netherlands	SP: 206, RP: 54 (26% follow-up)	Paper-based questionnaires, medical records	To assess the willingness of Type 2 diabetes mellitus patients to participate in a combined lifestyle intervention
5	Ryan and Watson [65]	2009	Comparing welfare estimates from payment card contingent valuation and discrete choice experiments, Health Economics	Attendees of a family planning clinic, UK	SP: 142, RP: 111 (78% follow-up)	Paper based questionnaire	To assess the willingness to pay of women to receive chlamydia screening
6	Chua et al. [61]	2016	External validity of discrete choice experiment: findings from a field experiment. Conference paper.	Attendees of pharmacies in UK	SP: 423 RP: 258 (61% follow-up)	Computer tablet	To explore patient preference for pharmacy-based health checks

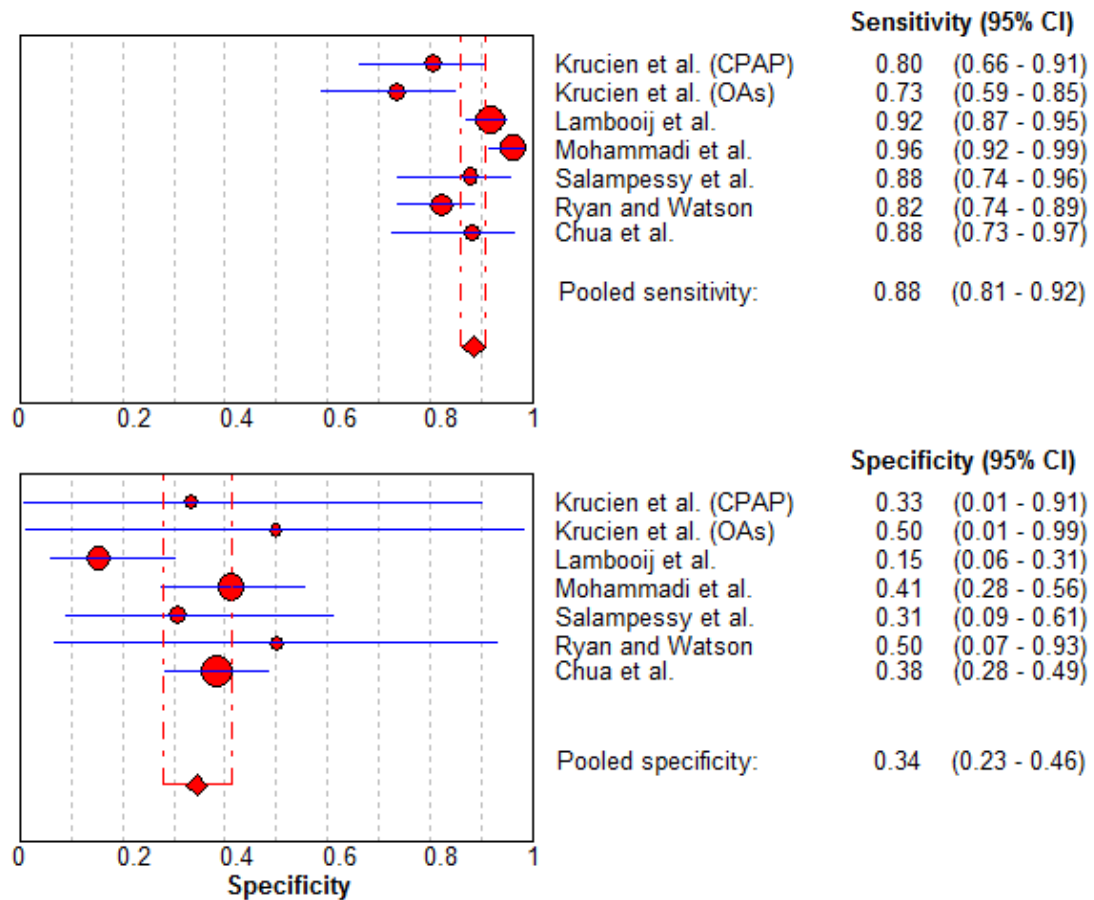
7	Kruk et al. [66]	2009	Women's preferences for place of delivery in rural Tanzania: a population-based discrete choice experiment, American Journal of Public Health	General population survey (household), Kasulu District, Tanzania	SP: 1,205	Paper-based questionnaires. RP data from census	To evaluate health-system factors which influence women's delivery decisions
8	Linley and Hughes [67]	2013	Decision-makers' preferences for approving new medicines in Wales: a discrete-choice experiment with assessment of external validity, Pharmacoeconomics	Past and present members of the All Wales Medicines Strategy Group (AWMSG)	SP: 41	Anonymous online questionnaire	To explore the preferences of the AWMSG appraisal committee and appraisal sub-committee for specific new medicines adoption criteria

Table 2: Extracted data for individual-level meta-analysis

No.	Authors	Outcome	True Positives	True Negatives	False Positives	False Negatives	Accuracy	Sensitivity	Specificity	PPV	NPV
1	Krucien et al.	CPAP	37	1	2	9	0.78	0.80	0.33	0.95	0.10
2	Krucien et al.	OAs	36	1	1	13	0.73	0.73	0.50	0.97	0.07
3	Lambooij et al.	All Outcomes	191	6	33	17	0.80	0.92	0.15	0.85	0.26
4	Mohammadi et al.	All Outcomes	147	21	30	6	0.82	0.96	0.41	0.83	0.78
5	Salampessy et al.	All Outcomes	36	4	9	5	0.74	0.88	0.31	0.80	0.44
6	Ryan and Watson	All Outcomes	88	2	2	19	0.81	0.82	0.50	0.98	0.10
7	Chua et al.	All Outcomes	30	36	58	4	0.52	0.88	0.38	0.34	0.90
8	Kruk et al.	All Outcomes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
9	Linley and Hughes	All Outcomes	25	12	N/A	N/A	0.64	N/A	N/A	N/A	N/A

N.b. Kruk et al. and Linley and Hughes do not contain sufficient data for inclusion in a meta-analysis

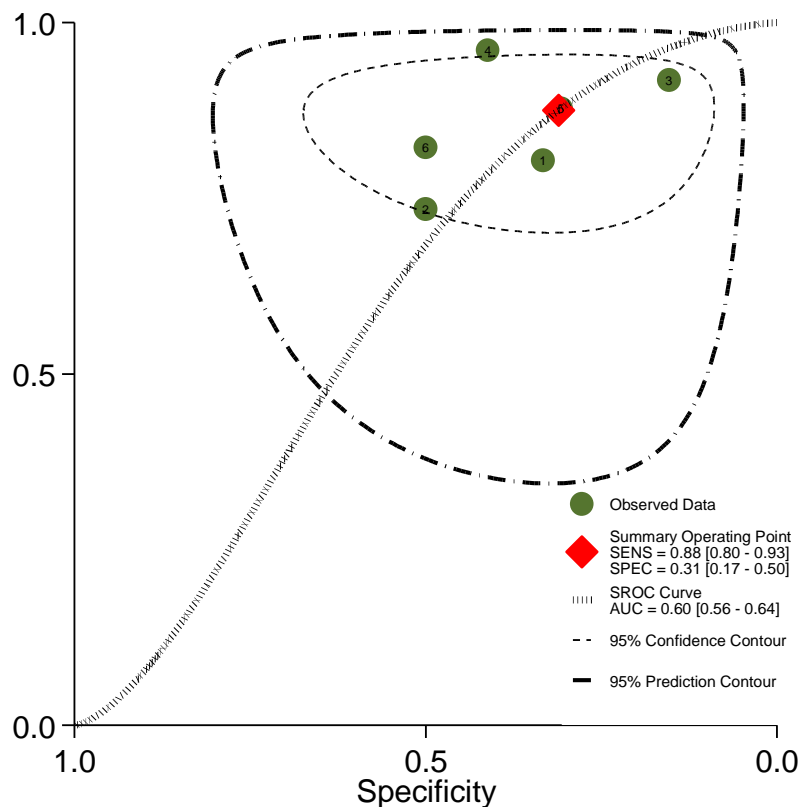
Figure 3: Synthesis of Sensitivity and Specificity of DCE predictions



Visual examination of results, shown in Figure 3, suggests that there was substantial between-study variation. The quantity I^2 statistic describes the percentage of total variation across studies which can be attributed to heterogeneity rather than due to chance, where an I^2 of 0% indicates that there was no heterogeneity between studies while an I^2 of above 50% suggests substantial heterogeneity [54, 68]. The I^2 estimates for sensitivity and specificity are 64% and 58% respectively, indicating that while there was substantial heterogeneity in both measures, estimates of sensitivity were subject to greater variation. Finally, we assessed publication bias through Egger's test which suggests no evidence of publication bias ($p=0.56$). However the capacity for this test to detect publication bias from a limited number of small studies is limited [56].

Under the presence of heterogeneity, summary receiver operating characteristic (SROC) curves can be used to display the results of syntheses where the higher the combined sensitivity and specificity of a test (i.e. the greater true positive rate), the closer the SROC curve will be to the top left of the SROC space [53]. Figure 4 shows the SROC for included studies, where the curve represents the relationship between the true and false positive rates across studies and was fitted to the data through least-squares regression [69]. The area under the SROC curve (AUC) can be a useful summary statistic of predictive ability, and the AUC we present in Figure 4 (0.60 [95%CI: 0.55, 0.64]) provides further evidence that DCEs have a moderate ability to predict choices; although there are no firm limits for “good” AUCs, meta-analyses of diagnostic tests infer a similar conclusions [70, 71].

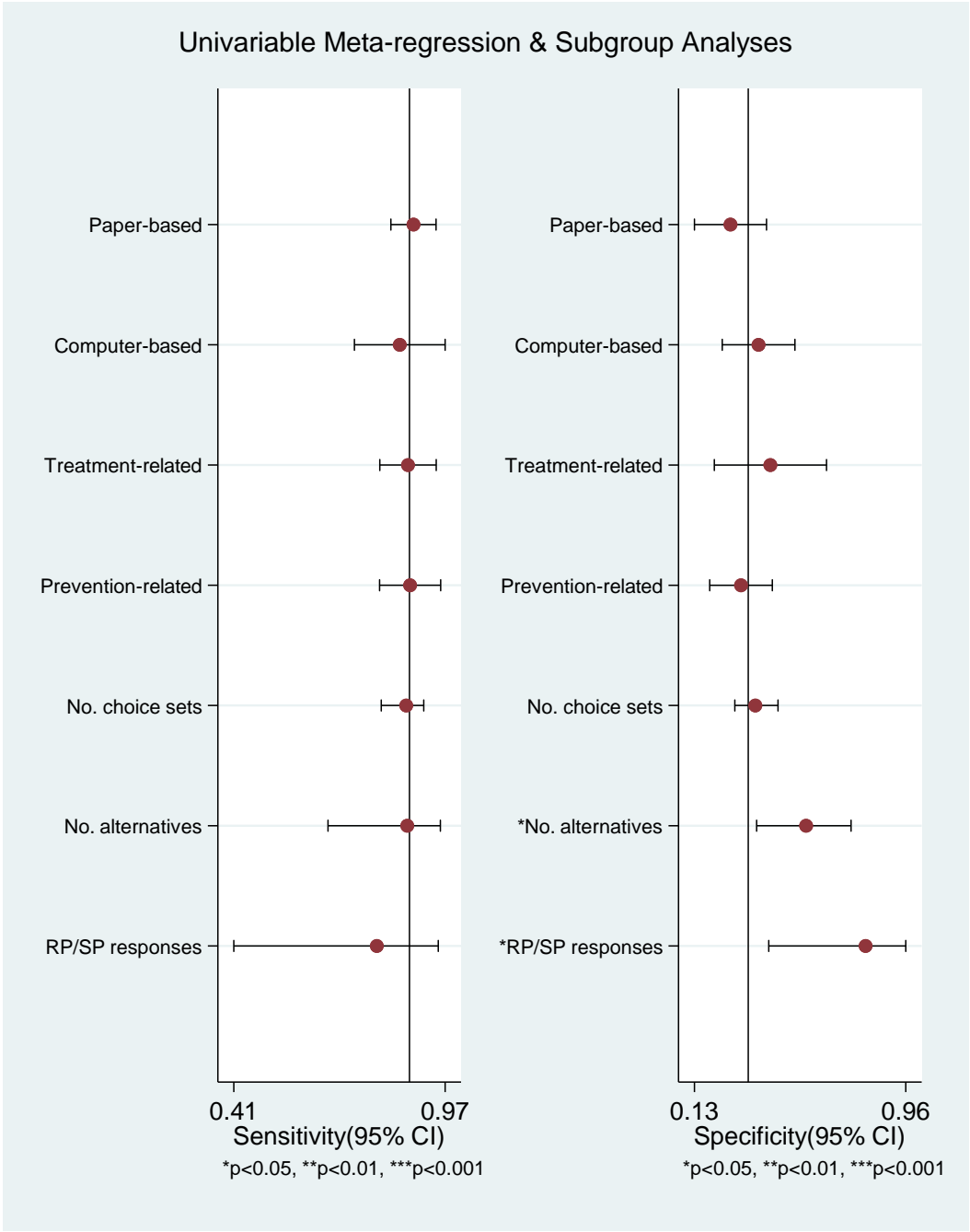
Figure 4: Summary Receiver-Operator Curve (SROC) of included studies



Finally, the results of univariable meta-regression are presented in Figure 5 and show that, even among the small number of studies, the specificity of DCE predictions is

significantly and positively associated with the SP/RP response rate, alongside the number of alternatives shown in choice tasks. No factor is significantly associated with greater or lower sensitivity. These results will become more precise and allow greater influence as more studies are published assessing the predictive ability of DCEs.

Figure 5: Meta-regression results



Discussion

This paper reports the results of a systematic literature review and meta-analysis and proposes a method to strengthen predictions made from DCE data. The systematic review identified seven studies as meeting the inclusion criteria. The meta-analysis of six studies with individual-level data found that DCEs have moderate, but not exceptional, accuracy when predicting health-related choices. Pooled sensitivity and specificity estimates were 88% (95%CI: 81%, 92%) and 34% (95%CI: 23%, 46%) respectively. All DCEs included in this review were exploring opting-in behaviours, and the mean observed uptake of options across all studies in this review was high at 76% (638 out of 844 observations). Only one study reported a measure of uncertainty around uptake predictions. The sensitivity of predictions was found to be greater than their specificity, suggesting that DCEs are better at predicting who would opt-in to a health-related decision rather than who would not. Overall, the review found very few studies comparing DCE predictions to observed choices at an individual level, and this is a key priority for future research.

We explored heterogeneity through use of meta-regression by incorporating study-level characteristics into bivariate mixed effects models, and found evidence that the RP/SP follow-up rate and the number of alternatives presented to respondents were positively associated with estimates of specificity, but not sensitivity. This study, being the first to synthesise evidence on the predictive ability of DCEs, is the first to show the extent of the heterogeneity in specificity when predicting behaviours, and care is needed when interpreting the results of DCE predictions. Due to the low number of studies in the literature, this analysis was underpowered and future research should focus on identifying the determinants of DCE external validity in order that DCEs and prediction methods give predictions with the greatest accuracy.

The finding that opt-in predictions from DCEs are reliable is useful for planning interventions and programmes. This quantification of how well DCEs predict behaviour could be used to explicitly account for uncertainty in DCE predictions, for example by using the pooled sensitivity point estimate and confidence intervals from this study to give upper- and lower-bounds of opting-in behaviours. Accounting for the variation in DCE prediction accuracy in this manner would make for more robust uptake and impact models. Although the pooled specificity estimate suggests that DCEs are not good predictors of opting out behaviour (i.e. should not be trusted when predicting that someone will not uptake a product or service), the pooled sensitivity estimate was relatively high and precise making it suitable for this application.

When considering how useful DCEs are in predicting behaviour, we must consider the alternative data sources available to decision makers. When predicting the demand for new health products or services, there is likely to be almost no information to base these forecasts on. One option is to run a pilot study or demonstration project; however, even on a small-scale, these can be both expensive and time-consuming. Another option would be to canvass expert opinion; however, even experts with the best of intentions can be incorrect or biased in their estimates. In such instances, DCEs can provide a relatively accurate and cost-effective option to predict individual choices. DCEs have been proposed for use to parameterise uptake and use parameters in health economic modelling[15], and if used for this purpose, parameter uncertainty could be partly accounted for using estimates from this review to adjust uptake estimates.

There may be some reasons why observed choices may be different to those predicted by DCEs. Firstly, the information presented in DCE choice tasks is necessarily a simplification of reality. Even in the case of high-quality DCEs, there are likely to be unobserved attributes present in real life decisions that were not, or poorly, accounted for in the DCE. Where these unobserved attributes influence the decisions of

participants, stated and revealed preferences will be based on heterogeneous choice attributes and may diverge. Even high-quality DCEs are unlikely to fully capture all relevant attributes of choice.

Secondly, DCE predictions may suffer from the intention-behaviour gap where individuals do not always ultimately behave in ways which they might intend to [72, 73]. For example, when people are a long way ahead of making a choice, they are more likely to commit to a substantial course of action (such as giving up smoking), however as they move closer to the choice situation they are more likely to choose the smaller reward (have a cigarette). This hyperbolic discounting suggests the passage of time changes the perception of the situation and choices, potentially explaining variation between DCE predictions and actual behaviour .

Results assume that there is a generalisable and measurable concept of DCE external validity. However this review was limited by the small number of studies identified which met the inclusion criteria. This meant that we were unable to undertake a meaningful analysis of where DCEs may provide more or less accurate predictions. For example, Ryan and Watson [65] find that a DCE for chlamydia screening has a high false negative rate (where more people screened in reality than predicted in the DCE), whereas Mohammadi et al. [59] find a high false positive rate of DCEs predicting treatment for tuberculosis (where the DCE over-predicted successful treatment). With a larger number of studies, it would have been interesting to explore whether such divergent results may have been down to study context (treatment requires continued adherence and not just a one-off action), cognitive biases (perhaps social desirability bias to predict successful treatment or not disclose demand for a chlamydia test outside of a consultation environment), or other reasons.

The meta-analytic tools used in this review are often employed to assess diagnostic tests, with the data normally used to assess these tests gathered in strictly controlled

environments. In contrast, the DCEs in this study cover a range of health choices across a broad range of populations, and it is perhaps no surprise that there was substantial heterogeneity between studies. Finally, predicted probabilities are just one interpretation of DCE results. Although probabilities are calculated using the coefficients of DCE models, this review explores just one interpretation of DCE results.

When compared against existing quality assessment tools, the quality of the included studies was high. However, when assessed against the additional external validity criteria, all but two studies were substantially prone to selection bias. As none of these studies gave any detail as to how participants were selected for follow-up, we are unable to fully assess how reliable these estimates might be.

A limitation of this review is the assessment of DCE predictive ability, which is just one facet of external validity. Assessing the external validity of WTP estimates was beyond the scope of this review, whilst the external validity of WTP estimates have been robustly assessed in three systematic reviews and meta-analyses since 2004 [36-38]. In addition, included studies must have been able to define participants' choice sets in the real world, implicitly limiting the scope of this review to predictions of choices within choice sets which can be represented consistently in a stable manner across real-world and hypothetical tasks e.g. uptake of a test, but not adherence to a treatment over time.

Although the sample size of included studies was incorporated in the standard error around pooled estimates, we are not able to account for potential publication or selection biases. The pooled sensitivity estimates are based on a multi-stage follow-up – participants must initially consent to participate in a DCE, then be successfully followed up to ascertain whether or not they engaged in a predicted behaviour. A recent meta-analysis indicates that the response rates to DCE surveys is often relatively low, and varies according to contextual factors such as the number of attributes or population surveyed [74]. This review could not incorporate divergent choices from those who did

not respond to DCEs in these samples, nor those who were lost to follow-up. Non-responders or those lost to follow-up may be systematically different from the included sample. Finally, we did not assess the internal validity of included studies. Although DCEs may vary in their predictive power absolute terms, the choice modelling literature suggests that their ability to give reliable data on the relative impact of some factors on choices is much more robust.

Conclusion

This study sought to systematically review the external validity of DCEs and is the first to synthesise studies assessing the predictive ability of DCEs in health. Seven studies were identified as meeting the inclusion criteria, and a meta-analysis of six studies with individual-level data found that DCEs have moderate, but not exceptional, accuracy when predicting health-related choices. Pooled sensitivity and specificity estimates were 88% (95%CI: 81%, 92%) and 34% (95%CI: 23%, 46%) respectively. This review and meta-analysis suggests that DCEs can be useful in predicting real-world behaviour, and provides important estimates of sensitivity and specificity which can be explicitly incorporated into impact and economic models. There is a substantial need for more evidence on how DCE predictions compare to real-world choices.

Supplementary material S1: Criteria for assessment of study quality

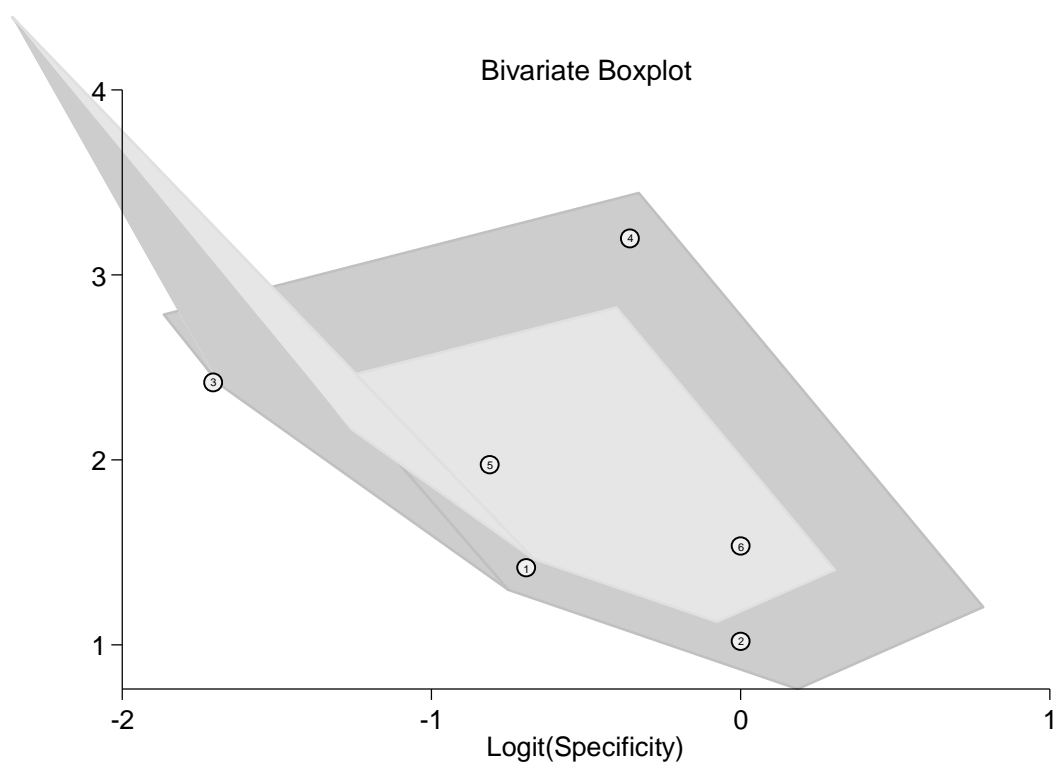
Section	Criteria	Justification
Choice Task Design	Choice of attributes and levels grounded in qualitative work with target population	Attributes and levels should be salient to the target population to ensure comprehension and engagement with the choice task
Choice Task Design	No conceptual overlap between attributes	Attributes should be conceptually distinct and vary independently of each other, otherwise effects will not be independent
Choice Task Design	Uni-dimensional attributes	Attributes that encompass several aspects of an attribute introduce variability into the choice process as participants may focus on different aspects and the resulting preferences can only be interpreted as being for all dimensions
Choice Task Design	Inclusion of an opt-out or status quo option or justification of forced choice	Choices that force participants to accept an unappealing choice are likely to lead to overestimation of preferences
Conduct	Piloting conducted amongst target population	Validity of choice task design and questionnaire features should be tested with participants from target population and subgroups
Conduct	Target population(s) appropriate for research objective	Preferences of target population should be sufficient to answer research objective
Conduct	Sampling frame representative of target population	Sampling frames that exclude part of the target population may lead to bias in preferences
Analysis	Any pooled analysis from different subgroups appropriate	Pooled analyses from very heterogeneous subgroups may mask marked differences in preferences
Analysis	Econometric model appropriate for choice task design	Model should be appropriate for the choice task and number of alternatives presented to participants
Analysis	Econometric model accounts for serial correlation of choices	As multiple observations are obtained from each participant, the econometric model should take account of panel nature of data to avoid overestimation of the differences between preferences
Analysis	Relative attribute effects compared using a common metric	Preferences for different attributes cannot be compared directly using parameter estimates due to confounding with the underlying utility scales
External validity	The same available set of alternatives are available in both environments	For predictions to be valid, participants must have the opportunity to choose from the same alternatives in both RP and SP choices

Section	Criteria	Justification
External validity	Linear-in-parameters evaluations	Models which are non-linear in parameters may give misleading results
External validity	Using the identical full information set of attributes in both environments	If participants are presented with more or less information in RP or SP tasks, this may bias results
External validity	Common utility maximising decision rule implicit in the MNL formation	To remain grounded in random utility theory (RUT), the participants must be assumed to make decisions based on the alternative which gives them the greatest utility
External validity	Revealed preferences are obtained for all, or from a random subset, of respondents	Where revealed preferences are elicited from a non-random subsample of participants, selection bias may distort results

Supplementary material S2: Quality assessment

Section	Criteria	Krucien et al.	Lambooi et al.	Salampey et al.	Ryan and Watson	Mohammadi et al.	Chua et al.	Kruk et al.	Linley and Hughes
Choice Task Design	Choice of attributes and levels grounded in qualitative work with target population								
Choice Task Design	No conceptual overlap between attributes								
Choice Task Design	Uni-dimensional attributes								
Choice Task Design	Inclusion of an opt-out or status quo option or justification of forced choice								
Conduct	Piloting conducted amongst target population								
Conduct	Target population(s) appropriate for research objective								
Conduct	Sampling frame representative of target population								
Analysis	Any pooled analysis from different subgroups appropriate	N/A (no subgroups)	N/A (no subgroups)	N/A (no subgroups)	N/A (no subgroups)	N/A (no subgroups)	N/A (no subgroups)	N/A (no subgroups)	N/A (no subgroups)
Analysis	Econometric model appropriate for choice task design								
Analysis	Econometric model accounts for serial correlation of choices								
External validity	The same available set of alternatives are available in both environments	N/A (unlabelled DCE)							
External validity	Linear-in-parameters evaluations								
External validity	Using the identical full information set of attributes in both environments								
External validity	Common utility maximising decision rule implicit in the MNL formation								
External validity	Revealed preferences are obtained for all participants, or from a random sample of respondents								
	Meets criteria								
	Unclear								
	Does not meet criteria								
	N/A								

Supplementary material S3: Bivariate boxplot of sensitivity and specificity estimates



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Results from updated search in January 2018

The searches conducted for this paper were re-run in January 2018. No additional studies were found comparing revealed and stated preferences within individuals in a health context. A number of changes were made to the paper during the peer-review process, including the updating of references for Chua et al. and Mohammadi et al. which were initially included in the review as conference presentations, but later updated. A meta-regression was also included.

In this update, an additional 1,913 studies were identified (PubMed: 157, EMBASE: 66, CINAHL: 169, Econlit: 143, Social Policy and Practice: 2, and Science Direct: 1,376). Of these, 254 were duplicates. None of the remaining 1,659 studies met the inclusion criteria, with 1,253 omitted at title screen and 406 at abstract screen.

Implications for thesis

The most substantive implication of these for this thesis is that DCE predictions can be used to predict health-related behaviours. We use this approach in results paper R1 to predict the uptake of a range of MPTs, and in results paper R3 to predict risk compensation among FSWs using an effective HIV prevention product. In both cases, we take care to conduct sensitivity analyses of parameters taken from DCE predictions to ensure that model results are not unduly influenced by uncertainty arising from DCE predictions.

Chapter 5: Additional information on the formative phase of DCE development

Development of the products DCE

The preceding protocol paper gives an overview of the formative work conducted for the development of the products DCE, alongside survey implementation methods. This section gives additional information on how the final design of the products DCE was created. The next section describes the design process for the second FSW DCE.

Development of attribute long-list

Results from qualitative work carried out for a 2005 study[1] were used alongside lessons learnt in the development and application of this earlier DCE[2] to identify a set of product attributes which are likely to be important to people, albeit ten years later. The FGDs mentioned in the protocol were carried out among FSWs; however, focused on the development of a completely new second DCE presented in this thesis and did not explicitly cover product attributes. Instead, substantial piloting and engagement work was carried out which is described here.

A long list of nine potential attributes was developed. All attributes found to be consistently statistically significant in the 2005 analysis were included (HIV protection, pregnancy protection, ability to use in secret, and price). Through meetings with academic and fieldwork staff, I drew on the experience of collaborators to identify additional relevant attributes for different populations. Finally, I carried out a comprehensive literature review exploring:

1. What types of ARV-based prevention products have been developed or are under development?
2. What factors influence the success or failure of products already tested?
3. What are the key research areas for the next ten years?

A summary of this work forms the background material in chapter 1 of this thesis.

The 2005 study found that the most important factors in women's use of HIV prevention products was the extent to which they protected from HIV infection and pregnancy. Furthermore, there was notable variation in the utility these attributes offered to women in different life situations. Due to the strength of preference women displayed for both attributes, we opted to include them in this DCE.

As described in the correspondence published in the *Lancet Infectious Diseases*, presented earlier in this thesis, recent developments in HIV prevention have led to optimism that candidate MPTs may soon be developed[3-7]. We explicitly focused on the potential for MPTs in developing this DCE. Three levels of HIV protection were used – 55%, 75%, and 95% – reflecting variation observed in efficacy trials of products, alongside idealised products used in modelling exercises[8]. Pregnancy protection was represented by a two-level attribute (yes/no). Ideally, we would have included both as multi-level, continuous attributes but opted to display pregnancy protection as a binary attribute to reduce complexity, after comments during piloting.

The "ability to use in secret" attribute was included in 2005 due to qualitative data suggesting that this was important to respondents. However, quantitative DCE results suggested that the significance of the secrecy attribute coefficient depended on the model specification used, and whilst the influence of the secrecy attribute on choices was small relative to others. Because the current study explores preferences for products with vastly different usage regimens and frequencies, I opted to fix the secrecy characteristic by product (giving participants information on whether a product could be used without a partner's knowledge in the explanation of products through an information sheet given to all participants). Therefore, the utility which is offered by using a product with or without a partner's knowledge is contained in the product-specific coefficient. This is a limitation of this study as it is not possible to separate the utility that secrecy may add in addition to that given intrinsically by products, for

example, how much more attractive a vaginal ring would be which allowed covert use. However, the nature of the products in development mean that it is impossible for secrecy to vary across products.

Frequency of use was considered an important characteristic because there is substantial variation across products. In addition, low levels of adherence to oral PrEP, microbicide gel, and vaginal ring products in PrEP trials to-date[9-11], particularly among younger women, mean that supporting adherent use has been identified as a critical part of the prevention cascade[12]. The decision to include frequency therefore came from the research question and potential implications for product development, rather than from inductive qualitative work.

Finally, side effects have been identified as a key driver of non-adherence among treatment users, and since the active ARV ingredient is similar in prevention (which to date is mostly based on tenofovir), it is thought that similar side effects might drive adherence (or non-adherence) in preventative products[4, 13]. The side effects attribute was particularly difficult to represent to respondents in a one-dimensional manner, and questions were raised around the severity of side effects to include (short-term, non-severe conditions such as dizziness, or long-term severe conditions such as liver failure) alongside the frequency with which these might occur. A number of iterations of the side effect attribute were explored in piloting with different representations of severity and frequency in written and pictorial form. Participants in pilot interviews were asked after carrying out the pilot DCE, a) whether shorter-term, less-severe side-effects were more important to their product choice than longer-term, more-severe side-effects, and b) which representations of potential side-effects were clearer to them, and for their suggestions to how side-effects could be accurately and consistently represented to a range of their peers. The development of the side-effects attribute can be seen in Figure 1.

Ultimately, respondents suggested that a) specific side-effects were clearer to understand than “mild/moderate/severe” side effect labels, b) that more immediate side-effects (such as stomach cramps or nausea) were more influential in choices than the more rare longer-term but more severe side-effects, and c) male- and female-specific images of side-effects were better understood than non-gendered, stick figure representations.

Refinement of attribute shortlist and selection

The long-list of attributes was reduced through intensive discussion with HIV and DCE experts at LSHTM, the University of the Witwatersrand (School of Public Health and Wits RHI), Bristol University, and PATH. Because of the necessity to reduce the number of attributes, the long list was reduced to five for further development and pre-piloting. Ultimately, these five attributes were used in the final DCE, however, throughout piloting we asked participants whether there were any important factors omitted and revised the presentation of attributes and levels a number of times.

The question of how many attributes is too many for participants to consider has had considerable attention in the DCE literature[14]. Including too few attributes increases the likelihood that important factors have been omitted. However, including too many may be cognitively demanding for respondents to consider all pieces of relevant information, increasing the likelihood of attribute nonattendance, or leading to protest responses as participants disengage with choice tasks[15, 16]. Although there has been a recent trend towards DCEs with greater numbers of attributes, the majority (70%) of DCEs identified in a 2012 systematic review contained between four and six attributes[14]. A practical limitation on the number of attributes came from the 10-inch screen of the tablet computers used in data collection, on which all alternatives and attributes had to be simultaneously displayed. This also constrained the choice between a labelled and unlabelled design, as discussed elsewhere.

A price attribute was not included as it became apparent during research that any roll-out of ARV-based prevention products would be provided free of charge by the South African Department of Health[17]. This is a limitation to this study as willingness-to-pay for PrEP products cannot be inferred from the data collected, however this increased the realism of choice tasks potentially increasing external validity.

An important consideration in choosing attributes is that of intra-attribute correlation, where different attributes are correlated perceptually by decision makers. For example, the price-quality heuristic suggests that decision makers may assume that higher priced alternatives display higher levels of quality, even though the two attributes may be statistically uncorrelated[15]. As the number of attributes were reduced from the long to the short list, we considered potential sources of inter-attribute correlation and tried to ensure that the final set of five attributes were conceptually independent from each other so that one is unlikely to act as a proxy for another.

Further considerations on the use of a labelled or unlabelled design

Including a label in DCEs adds a degree of realism to choices, as consumers do not select from a number of generic alternatives in real-life, but from among a labelled set of brands or types of good[15]. A recent study suggests that 22% of all choices in a cancer screening DCE were made on the label alone[18].

Though a design using product labels would be theoretically most appropriate for this study, this would have required six alternatives (five new products plus one opt-out) to be presented at one time on a small tablet screen. There was consensus during discussions with the project team that asking respondents to choose between six alternatives would make for a complex and tiring choice experiment. Therefore, we opted to reduce the number of alternatives presented to respondents to three (plus an opt-out), where one attribute represented product type. Product labels entered the DCE as levels of this attribute, rather than separate labelled alternatives.

This strategy means some loss of precision in estimates of product-specific constants as fewer choice data are collected for each label (now represented by the coefficient for each level of the effects-coded product attribute, instead of an alternative-specific constant), however, this may provide data of better quality overall through reducing participant fatigue.

Feedback and iteration

Once the short-list and early mock-up of representations (version 1 in Figure 2) had been generated, feedback was obtained from DCE experts at LSHTM (Mylene Lagarde) and the University of the Witwatersrand (Duane Blaauw). Feedback suggested a) exploring different representations of the HIV protection attribute (comparing a visual array of “people” to a pie-chart representing the degree of protection a product offers), b) representing pregnancy and STI protection as two-level attributes to reduce complexity, and c) explore different representations of side-effect severity and probability. Changes to the DCE as a result of these comments can be seen in version 2.

Version 2 of the DCE was presented in a research seminar to around 20 researchers (working mostly in HIV) at Wits RHI in Johannesburg in June 2015. There was a consensus that the five short-listed attributes were relevant and meaningful to the choice task in that context, whilst the mix of attributes chosen would provide interesting policy and product developmental insights. There were a range of views on the side-effects attribute, with specific concerns covering a) how to represent the frequency and severity of side-effects as a one-dimensional attribute as recommended in the literature[19]; b) what side effects might impact demand for a product (severe but rare side effects such as liver failure, or milder and more common side effects such as nausea or stomach cramps); and c) how best to represent side-effects (visually or through words).

Further feedback was taken on the visual representation of some attributes, particularly that HIV protection would be best represented as a risk array, which is the most popular means of representing risk in published DCEs[20]. In addition, local experts suggested that the acronym "STI" would be understood well, and be more meaningful to participants than "other infections" – this later turned out to be the case in piloting. Because of suggestions from this meeting, we produced version 3 of the DCE in Figure 2, which was used for pre-piloting.

Pre-piloting

Pre piloting was carried out in the general population in two rounds among 8 adult females, 5 adult males and 4 adolescent females, described in Table 1:

Table 1: Pre-pilot dates and participants

Pre-pilot round	Dates	Participants
Round 1	26 th -27 th August 2015	6 adult females, 3 adult males
Round 2	3 rd September 2015	2 adult females, 2 adult males, 4 adolescent females

Pilot participants were identified from a convenience sample of participants from the three groups. FSWs were not specifically sampled in this pre-piloting stage. Because FSWs are a subset of the adult female population, FSW programme experts indicated that the insights of pre-piloting among this group would be sufficient to negate the need for pre-piloting among FSWs. Nevertheless, during the later FSW-specific pilot, we ensured that respondent understanding was comprehensively explored and ensured there was time and resources available to re-design the product DCE for this population if required.

At this point, after discussion with fieldworkers and pilot participants, we opted for interviewer administration of the survey, as opposed to respondents entering data directly into the tablet computer. Although this may increase acceptability biases in

reporting of sensitive behaviours (such as age at first sex, condom use, or number of sexual partners[21-23]), interviewers were able to thoroughly explain the DCE task and ensure that participants were making careful and informed decisions. Through encouraging participants to “think aloud” through all choices (shown elsewhere to increase the external validity of stated preference tasks[24, 25]), interviewers were able to assess the degree to which participants were understanding and engaging with choice tasks.

The resilience of this method was shown in final piloting. For example, a female respondent chose the condom opt-out in all but one choice set. When probed by the interviewer, the respondent said that she wanted the full protection that condoms offered across all attributes. She still looked at every alternative but chose condoms eventually, except when a vaginal ring offered the same protection and side-effects profile with a reduced frequency of use. In another instance, one male appeared to be choosing oral PrEP in each task, regardless of how attributes compared to that of an injectable. When asked to “think-aloud” through his decision-making process, the respondent revealed a substantial dislike for injections, over and above the importance of other product characteristics. Where one choice set had three injection alternatives with an unprotected opt-out, the respondent chose the highest HIV efficacy.

Also at this stage, I opted to reduce the number of choice tasks presented to participants from 15 to 10 after interviewer feedback that the tasks became boring to participants after 8-10 choice tasks. Interviewers reported that participants were, in the most part, engaged with the first 8-12 choice sets, however became fatigued with the tasks towards the end of the DCE, either making choices based on just 1-2 attributes, or by choosing largely at random.

Decreasing the number of tasks reduced the quantity of choice information gathered from each respondent, resulting in less precise preference estimates. However,

minimising tedium in the choice tasks could have increased the quality of information captured. Ignoring some attributes in a choice task, termed attribute non-attendance, is an example of choice behaviour which violates the axioms underpinning random utility theory (that participants choose the alternative offering the greatest utility as a sum of its individual attributes)[15]. Choosing responses at random can be considered an extreme form of attribute non-attendance. Either behaviour will bias choice model parameters towards the null, reducing the efficiency of models and the information gained from the DCE[15, 26].

However, reducing the number of DCE tasks also reduces the amount of information obtained from each participant. To assess if the reduction in precision as a result of reducing the number of choice tasks could meaningfully reduce the statistical power of the DCE, D-error minimising designs with 10 and 15 tasks were generated in NGENE software[27], and the *Sp* value examined – an estimate of the minimum sample size required to obtain statistically significant parameters in a discrete choice model using parameter priors normally obtained from piloting work. Appendix V shows the NGENE output from both designs; the 15-task design has an expected sample size needed for significant parameters of 63 participants, whilst the 10-task design would require a sample size of 134. Since the total sample size in each survey group was 200, the 10-task DCE was deemed sufficient on this basis.

A number of changes to attribute presentation were made during piloting. Firstly, the use of a red cross to signify no STI protection was found to be confusing when compared to the use of a similar red cross to signify contraceptive properties in the pregnancy attribute. Interviewers themselves suggested incorporating a tick, separate from an image of a non-pregnant woman, to represent contraceptive properties. This was in contrast to a red cross alongside an image of a pregnant woman to indicate a lack of contraceptive protection. Feedback from piloting suggested that interviewers and

participants found this representation (Figure 1 – panel B) easier to explain and understand than previously (Figure 1 – panel A).

Figure 1: Changes to representation of contraceptive attribute

Panel A – Initial representation



Panel B – Final representation after changes



The frequency of use attribute was further refined through a) changing the denominator of use to be consistent across non-coital usage as "number of uses in a year", and b) text being placed inside a box and highlighted such that the attribute stood out alongside pictorial representations of others. We explored the use of graphics representing frequency of use, however, participants indicated that the text representation simpler to understand, and it was not possible to unambiguously represent coital use in this manner. A limitation of the analyses presented in this thesis is that they do not explore the potential for attribute non-attendance to occur, where text attributes are ignored by participants in favour of those represented by pictures.


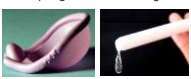























Finally, representing side-effects well was a challenge throughout the design process. Because of comments from local experts, we included a categorical four-level side-effects attribute: no side effects, dizziness, stomach cramps, and nausea. These were a) reported side effects of tenofovir use, b) symptom based and therefore easily understood, and c) familiar to most participants thus requiring less abstract reasoning during the DCE.

These were chosen instead of longer-term side-effects such as liver complications or reductions in bone density, which have also been recorded with tenofovir use[28, 29]. This was largely because long-term side effects require a substantial amount of abstract thinking on the part of respondents, which would have been challenging for respondents as part of an already complex DCE. In addition, to adhere to DCE best practice and only include one-dimensional attributes[19], each long-term condition would require four separate attributes to represent the severity, probability and nature of side-effects.































This decision also meant that, rather than including multiple attributes to represent different side-effect aspects, a single attribute was required to convey the symptoms of each side-effect. Although the reported frequency of side-effects varied slightly across the three included, we opted to fix the frequency at which all three would "occur" as the most frequent reported in the literature[29]. In round one of pre-piloting this was just explained to participants by interviewers, however, some respondents repeatedly clarified this point throughout the tasks. As a result, for later rounds of the pilot, and in the final DCE, we included a frequency array (as displayed in version 4). This served to make the 1/60 chance of side effects occurring more salient to participants, whilst the fixed frequency across side effect levels meant the attribute was still one dimensional.

Figure 2: Iterations of DCE formatting













Version 1:

Choice:	A	B	C	D	E	F
Product	Oral PrEP 	Diaphragm and microbicide gel 	Microbicide gel 	Vaginal ring 	Injection 	
HIV protection	75% risk reduction  15 of 20 women remain HIV negative	75% risk reduction  15 of 20 women remain HIV negative	75% risk reduction  15 of 20 women remain HIV negative	95% risk reduction  19 of 20 women remain HIV negative	95% risk reduction  19 of 20 women remain HIV negative	Neither, I would do the same as the last time I had sex
Pregnancy prevention	55% reduction in pregnancies  9 of 20 women become pregnant	55% reduction in pregnancies  9 of 20 women become pregnant	55% reduction in pregnancies  9 of 20 women become pregnant	Does not prevent pregnancy  All 20 women become pregnant	Does not prevent pregnancy  All 20 women become pregnant	
Frequency of use	Twice every week	Every time you have sex	Every time you have sex	Once every month	Once every 3 months	
STI protection	 Prevents half of STIs	 Prevents no STIs	 Prevents half of STIs	 Prevents no STIs	 Prevents no STIs	
Side effects	 5 of 20 people feel side effects	 1 of 20 people feel side effects	 1 of 20 people feel side effects	 5 of 20 people feel side effects	 1 of 20 people feel side effects	






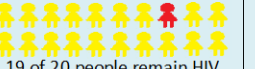










Version 2:

	Oral PrEP	Diaphragm and Microbicide Gel	Microbicide Gel	Vaginal ring	Injection	Condom
Product						
HIV protection	Risk Reduced by 75% 	Risk Reduced by 55% 	Risk Reduced by 95% 	Risk Reduced by 75% 	Risk Reduced by 75% 	Risk Reduced by 95% 
Pregnancy prevention	Cannot prevent pregnancy 	Can prevent pregnancy 	Can prevent pregnancy 	Cannot prevent pregnancy 	Cannot prevent pregnancy 	Can prevent pregnancy 
Frequency of use	Once every 3 weeks	Every time you have sex	Every time you have sex	Once every 3 months	Once every month	Every time you have sex
Protection against other infections	Prevents other infections 	Does not prevent other infections 	Does not prevent other infections 	Prevents other infections 	Prevents other infections 	Prevents other infections 
Side effects	Some Side Effects 	Some Side Effects 	No Side Effects 	Large Side Effects 	Large Side Effects 	No Side Effects 

Version 3:

1	A	B	C	Nothing
Product	Injection 	Oral PrEP 	Oral PrEP 	
HIV protection	55% risk reduction  11 of 20 people remain HIV negative	75% risk reduction  15 of 20 people remain HIV negative	95% risk reduction  19 of 20 people remain HIV negative	
Pregnancy prevention	Does not prevent pregnancy 	Does not prevent pregnancy 	Prevents pregnancy 	
Frequency of use	Use once every year	Use three times per week	Use once per week	
Protection against other infections	STI Protection Prevents STIs	STI Protection Prevents STIs	STI Protection Does not prevent STIs	
Side effects	 No Side Effects	 Stomach cramps/pain	 Nausea/feeling sick	

Version 4 (female):

1	A	B	C	Nothing
Product	Vaginal ring 	Microbicide Gel 	Microbicide Gel 	
HIV Protection	75% risk reduction  15 of 20 people remain HIV negative	95% risk reduction  19 of 20 people remain HIV negative	75% risk reduction  15 of 20 people remain HIV negative	0% risk reduction  0 of 20 people remain HIV negative
Pregnancy Protection	Does not prevent pregnancy 	Does not prevent pregnancy 	Prevents pregnancy 	Does not prevent pregnancy 
Frequency	12 times per year	365 times per year (daily)	Every sex	Never
STI protection	STI Protection Prevents STIs	STI Protection Does not prevent STIs	STI Protection Does not prevent STIs	STI Protection Does not prevent STIs
Side Effects	 Dizziness	 Stomach cramps/pain	 Nausea/feeling sick	 No Side Effects

Version 4 (male):




























1	A	B	C	Nothing
Product	Injection 	Injection 	Oral PrEP 	
HIV protection	95% risk reduction  19 of 20 people remain HIV negative	75% risk reduction  15 of 20 people remain HIV negative	95% risk reduction  19 of 20 people remain HIV negative	0% risk reduction  0 of 20 people remain HIV negative
Pregnancy prevention	Does not prevent pregnancy  	Prevents pregnancy  	Prevents pregnancy  	Does not prevent pregnancy  
Frequency of use	1 time per year	2 times per year	12 times per year	Never
Protection against other infections	 Does not prevent STIs	STI Protection Prevents STIs	 Does not prevent STIs	 Does not prevent STIs
Side effects	  No Side Effects	  No Side Effects	  Dizziness	  No Side Effects

Table 2: Attributes included in products DCE

Attribute	Levels	Source	Reason
Products	Oral PrEP, microbicide gel, SILCS diaphragm and gel, vaginal ring, injection	Literature, expert opinion	Current and future product pipeline. Different time horizons for each product's development (i.e. injection ~10 years whilst PrEP is available in South Africa today)
HIV Protection	55%, 75%, 95%	2005 DCE	Focus of study. Important determinant of demand in 2005 DCE
Pregnancy Protection	Yes, no	2005 DCE, expert opinion	Important determinant of demand in 2005 DCE. Reclassified as binary for simplicity in presentation.
Frequency of use	Coitally, daily, weekly, monthly, three-monthly, six-monthly, annually	Literature, expert opinion	Seen as important factor in studies exploring low adherence in ARV- based prevention trials[30]
STI Protection	Yes, no	Literature, expert opinion	Important in literature exploring the potential for MPTs[3, 4, 31]
Side Effects	Nausea, dizziness, stomach cramps	Literature, reports from PrEP studies	Concerns that adherence to prevention products might be inhibited by observable side-effects (i.e. shorter-term, non- severe events rather than longer-term severe side-effects such as liver failure). Levels taken from HIV treatment studies and trial reports[29, 32, 33]

Table 3: Attributes excluded from products DCE

Attribute not included	Potential levels	Source	Reason
Secrecy	Can be used in secret, Cannot be used in secret	2005 DCE	Levels likely to be fixed by product - a gel will always require partners' knowledge, whilst an injection could always be obtained covertly
Mode of delivery	Oral, vaginal, injection	Literature review	Fixed by product
Monitoring	None, weekly, monthly, quarterly	Literature review	Not identified as important by experts, or during piloting work
Forgiveness in regimen	High, medium, low	Literature review	Difficult for respondents to conceptualise and represent in DCE tasks, so dropped early in piloting
Purchasing location	Clinic, spaza shop, community outreach worker, pharmacy	2005 DCE	Since product distribution likely to only be through public clinics in the first instance, this was omitted to keep the number included low
Price		2005 DCE	In many DCEs, price attributes have dominated choice behaviours.[15] This was omitted to avoid this, and also represent the fact that products will likely be provided free of charge in South Africa.

Estimating unconditional demand

To improve uptake estimates in the cost-effectiveness analysis, paper R2, an opt-out alternative was included in choice tasks, allowing the estimation of unconditional demand. If we had not included an opt-out, and instead calculated conditional demand through forcing a choice between new products, we would have had greater precision in attribute coefficient estimates but not be able to predict uptake.

As mentioned briefly in the protocol, the opt-out alternative was presented as the characteristics of a male condom, or for using nothing, depending on whether or not a condom was used in the last sex act. This made the choice scenario more realistic, as its framing and choice set was based on the last sex act, but in doing so we assumed that condom users always preferred a condom over unprotected sex, and did not allow non-condom users to choose a condom. This may have led to underestimation of condom use, and biased estimates of new product cost-effectiveness towards being more cost-effective.

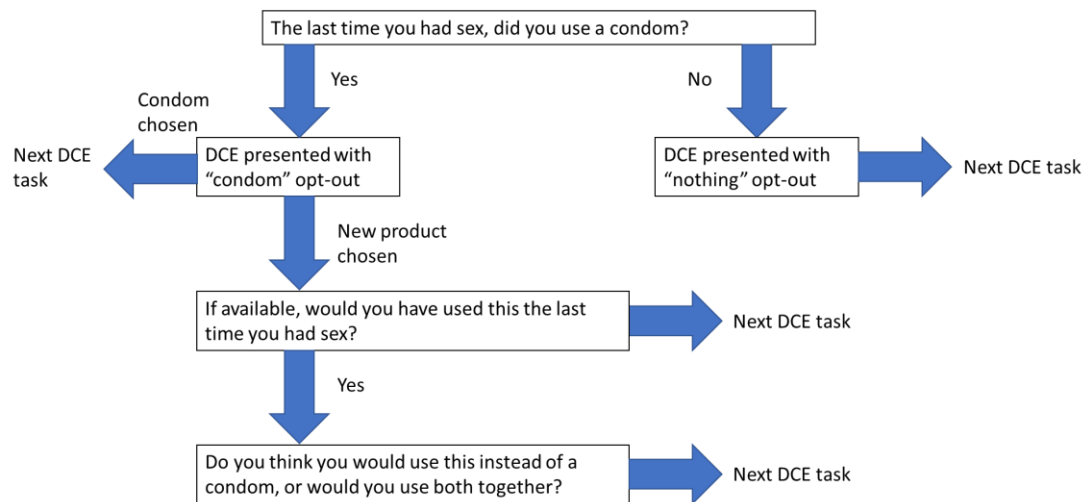
Estimation of condom substitution

Knowing whether the users of new products are also consistent condom users is critical to estimate their impact[34]. For example, if demand for new prevention products is solely among current condom users, the additional impact of new products will be minimal, particularly if users choose to use a new product instead of a condom. Conversely, if demand for new products is largely among non-condom users, the potential for additional benefit is high.

There are three steps to ensuring that this DCE captures sufficient information on respondents to estimate impact accurately, displayed in Figure 3. Firstly, the opt-out presented to participants is tailored to the product they report using in their last sex-act. This was carried out by programming the tablet computer to display a different opt-out alternative depending on a participant's answer to the question "the last time you had

sex, did you use a condom?" If yes, participants were shown an opt-out for each choice task containing the attributes of a male condom. If participants reported that a condom was not used, they could not remember, or did not wish to say, they were presented with an opt out of "nothing" with a set of attributes representing no protection against HIV, pregnancy or STIs and with no side-effects or frequency of use.

Figure 3: Representation of opt-out alternatives



When participants who reported using a condom in their last sex act chose one of the new products over the condom opt-out, they were asked a further question of "if available, would you have used this the last time you had sex?". If the answer to this question was yes, respondents were then asked "would you have used this instead of a condom, or would you have used both together?". With these data, it is possible to estimate substitution from condoms to new products, alongside uptake amongst non-condom users, however acknowledge that dual use of condoms with new products may be unrealistic.

Development of the FSW DCE

This section describes the development of the FSW DCE, a DCE to assess whether HIV prevention products will change FSW preferences for the supply of condomless commercial sex. Although a protocol was not published for this DCE, data collection was fully integrated within the FSW sample described earlier. Furthermore, many of the methods used are described in the results paper for this DCE, paper R3. Therefore, in this section I only provide information about the development of this DCE which is not included elsewhere, notably an overview of the qualitative work and piloting process, and refer the reader to the results paper (chapter 8 – Paper R3) and study protocol (Appendix IX) for further details.

The earlier literature review summarised economic evidence suggesting that there was a price premium for unprotected sex among female sex workers in multiple countries and contexts. Just one of these studies was in Africa (Kenya[35]), and there has been no work exploring the economics of commercial sex in South Africa. Furthermore, there has been no work in any context exploring the potential impact of effective new HIV prevention products on the market for commercial sex in any context.

This DCE was designed to elicit FSW preferences towards key client and commercial sex-act characteristics. We employ a repeated DCE design, where the same DCE is presented to each respondent twice – once with no framing, and a second time asking participants to choose as if they were fully protected from HIV.

Because a number of additional data on commercial sex acts were gathered among the FSW population, the survey was expected to take much more time among this population. Furthermore, the opportunity cost of FSW time was estimated to be greater than other populations due to their comparatively greater earnings. Therefore, the primary design consideration for this DCE was to minimise the time required to

complete the DCE, whilst making the choice scenarios engaging and easily understood to ensure good quality choice data.

The development process of the FSW DCE aimed to 1) identify what client and act characteristics are important to FSWs' decisions to engage in protected or unprotected intercourse; 2) explore how to best represent these attributes in a DCE; and 3) maximise efficiency in DCE data collection. Firstly, a long list of attributes was generated through a thematic analysis of two focus group discussions, with thirteen participants in each (two further focus group discussions were held during data collection to inform the analysis and interpretation of results). The attribute long list was supplemented and refined with the results of the literature review presented earlier in this thesis, alongside input from UK and South African experts in DCE methods and FSW populations.

Attribute and level development

Development of attribute long list

Qualitative focus group discussions

We carried out four focus group discussions (FGDs) with a heterogeneous mix of 9-13 participants in each. Participants were purposively sampled to obtain a mix of women working in hotels and on streets with the intention of stimulating a broad discussion. A thematic analysis of these FGDs led to the identification of important attributes in the choice context, specifically around client characteristics, and to explore which attributes may be affected by the introduction of effective products. The specific aims of the FGDs were to:

1. Explore how women conceptualise "good" or "bad" clients
2. Understand how condom use and price is negotiated with different types of client
3. Explore how perceived negotiation power in commercial acts relates to condom use and price agreements

To ensure that we obtained sufficient data from FGDs, considerable time was spent developing a concise and informative focus group discussion guide, which is presented in appendix VII. Developing the guide was an iterative process where the content and wording of each draft was tested and reviewed among members of the project team, before a final draft was reviewed by the FGD moderator from Progressus Research and Development.

Focus group discussion recruitment and procedures

In total, four FGDs were held among members of the target population for the DCE. FGDs in Springs and Brakpan were used to develop the DCE and survey, whilst two subsequent FGDs in Boksburg were used to give greater depth to the data alongside informing analysis and interpretation of data.

We used existing peer-outreach networks to recruit participants. Our collaborating institution, Wits RHI, provided mobile clinic services for FSWs in Ekurhuleni. The clinic travelled to a different location every Thursday, cycling through six locations. Active FSWs were referred to the Wits RHI clinic by peer educators in the area, who were themselves employed by an NGO, Center for Positive Care (CPC). With an introduction from Wits RHI, we approached the local CPC management and explained the objectives and method of our study. We were given permission to ask CPC peer-educators to a) assist in recruiting FSWs for the focus group discussions, and b) for a small number to participate in discussions themselves, as previous work by our data collection partners found the presence of peer-educators conducive to open and frank conversation.

An important aim of recruitment was to ensure a range of experiences in each discussion, and we recruited women of a range of ages and working environments (street-based and hotel-based workers). The literature suggests that the risks and rewards of sex work can vary substantially by context, whilst a heterogeneous set of focus group participants has been shown to encourage a nuanced discussion, with participants more likely to agree

on a common identity (i.e. belonging to the group of "female sex workers") whilst highlighting differences in their experience of that identity.[36, 37] Brown[38] suggests that the number of FGD participants should increase with the degree of heterogeneity between participants, with a maximum of around twelve. Because of the busy and transitory nature FSWs' working lives, we opted to invite more respondents than required to allow for some non-attendees. Ultimately, relatively high levels of attendance meant we had a maximum of 13 and a minimum of 9 participants in each FGD. The data from the FGD with 13 participants did not inhibit conversation or the quality of data.

We initially planned to integrate the FGD work alongside outreach clinic activities, however, were advised by peer educators that women would not be willing to give up more productive time on the days the clinic was present. Furthermore, we were advised that many FSWs would be busy working between Thursday evenings and Monday morning. We therefore scheduled focus groups midweek when a clinic was not present. To conduct the FGDs, we utilised the same location where outreach activities occurred; these offered a safe, confidential and secure space in which to carry out FGDs.

Once we had set a location and time for the FGD, peer-educators were asked to recruit women based on their schedule of providing outreach services that day. Through selecting which peer educators recruited for each group, we were able to achieve a mix of street- and hotel-based participants. We ensured that free transport was available for potential participants, however this was not required for any participant as FGDs were held in convenient locations.

As participants arrived at the FGD location, they were welcomed by a survey team member who offered refreshments. When the group were together the moderator explained the study in general; read out the guidelines for the discussion, as on the front of the FGD guide (i.e. speaking up when they felt they had something to say, not interrupting other participants); introduced specific topics for discussion; explained

why we had specifically asked for participants to attend; and that we were interested in their honest thoughts and opinions on the discussion topics. The informed consent form was distributed to participants and read out loud by the moderator; this form is included in appendix VI.

Participants were told that the discussions were confidential, that they could rely on the survey staff not to disclose what they said, and that the views that others express during the discussion should not be discussed outside of the group. The moderator told the group that they could use whatever name or nickname they wished, and we did not need to know their real identity. Finally, the moderator explained the presence and purpose of the two audio recording devices. If participants were still willing to participate in the discussion, the moderator and an additional survey team member went around the group individually, answering any further questions and, if required, assisted participants in completing the informed consent form.

The moderator informed participants that the audio recorders would turn on, explained once more that the discussion was recorded from this point, and obtained a verbal acknowledgement from the group. The moderator then began the discussion, first choosing which language(s) were most comfortable for people to speak in. Conversation was broadly framed around the discussion guide, with the moderator ensuring conversation flowed naturally whilst covering all relevant points. When the discussion ended, the tape was switched off and participants offered refreshments. As a token of thanks for their time, participants were provided with a R50 (approx. £2.50) voucher.

Role of candidate in FGDs

FGDs were carried out by a data collection consultant, Motlalepule Tsepe, a senior partner at Progressus Research and Development with over ten years of fieldwork experience. Although I did not attend the FGDs, I wrote the FGD discussion guide and worked intensively with the FGD moderator in days before each FGD to ensure the FGDs

were carried out correctly. Directly after each FGD, the moderator and I had a debriefing where we identified topics that were missed, alongside those which were discussed at too much length. The topic guide was not altered during data collection.

Analysis of FGD data

Due to time constraints between the completion of FGDs and the requirement to submit a final version of the DCE survey for final ethical review, a full analysis of the FGDs was not possible. Instead, a preliminary framework analysis was carried out in partnership with Robyn Eakle, a qualitative researcher at Wits RHI, who identified the following themes from the data. A fuller analysis of the FGDs was presented as a poster at the HIV Research for Prevention Conference in Chicago, USA on the 2016, which is included as Appendix X.

Refinement of attribute shortlist and selection

As with the refinement of the products DCE described above, the attribute long list for the FSW DCE was reduced through presentation to experts. The background survey among FSWs included additional questions on commercial sexual behaviour which were not asked to the general population. This meant that the DCE had to be intuitive and relatively quick to complete, particularly as it was being carried out twice with each FSW participant in addition to the products DCE.

Due to delays in finding local collaborators who could facilitate access to the FSW population, the development of the FSW DCE occurred after the products DCE had been finalised. We used this to our advantage by applying the lessons learnt in the development of the products DCE in our target population, notably that more than five attributes were difficult to represent clearly on the tablet screen, and that more than ten choice tasks in a DCE led to participant fatigue. The DCE lent itself to an unlabelled design due to the lack of overarching concepts of clients that FSWs choose between. Also at this stage, we decided to include an opt-out alternative to allow the estimation of

unconditional demand, and enable the simulation of choices to parameterise the dynamic transmission model in paper R4. Tables 3 and 4 detail the attributes included the final DCE and those omitted, respectively.

Table 4: Attributes included in FSW DCE

Attribute	Levels	Source	Reason
Price	<ul style="list-style-type: none"> • R100, • R200, • R400, • R800 	Economic literature, work in other SA FSWs[39], qualitative work	Primary research question to explore how price and condom choices change with PrEP introduction
Condom use	Male or female condom, no condom	Economic and social epidemiologic literature, qualitative work	Primary research question to explore how price and condom choices change with PrEP introduction
Type of sex	Vaginal, anal	Economic literature, pilot with peer-educators	Initially left out, but included after piloting comments. Different prices[40, 41] and HIV risk[42] associated with sex type
Perceived client HIV risk	You think this client has HIV, you don't think this client has HIV	Economic literature, expert input, piloting	Concordance with study aims, allows assessment of framing effect
Perceived client STI risk	You think this client has and STI, you don't think this client has an STI	Economic literature, qualitative findings piloting	Concordance with study aims, identified as relevant during qualitative work[43]

Table 5: Attributes excluded from FSW DCE

Attribute not included	Potential levels	Source	Reasons omitted
Handsome client	Handsome client, non-handsome client	Economic literature	Subjectivity of handsomeness, not identified as relevant during qualitative work, lack of relevance to study aims
Drunk client	Client seems drunk, client seems sober	Expert input, FGD results	Subjectivity of what "drunk" means, ubiquity of alcohol use in some settings, conflated with perceived STI/HIV risk
Client age	Client <25 years, client 26-40 years, client >41 years	Economic literature, expert input	Was not identified as relevant during qualitative work
Repeat client	Regular client, occasional client, new clients	Expert input, FGD results	Was identified as important during qualitative work, but conflated with perceived STI and HIV risk
Client risk	Client seems risky, client does not seem risky	Expert input, economic literature, FGD results	Separated after piloting to HIV and STI risk, conflated with risk of perpetrating violence

Estimating the impact of HIV prevention product use on act price and condom use were the primary objectives of the study. Condom use was included as a binary variable denoting male condom use or unprotected sex; female condoms were omitted here due to low reported use among FSWs during FGDs. The four levels of the price attribute were obtained from FGD information, alongside quantitative data collected in 2010 by Richter et al.[44].







We considered including several client characteristics as separate attributes: attractiveness, perceived inebriation, age, whether the client was new or a repeat client,

and client risk. As with the products DCE, the long list of attributes was presented in seminars at LSHTM and Wits RHI, where comments from experts led to the development of a four-attribute draft task from the long list of nine attributes.

We considered using images of client faces to represent client attractiveness, however, it was not possible to generate a set of faces to represent a scale of attractiveness which was consistent across potential respondents. The subjectivity of the client attractiveness attribute, alongside difficulties in justifying its inclusion when not directly contribution to a research question, meant that this was dropped before piloting. Client age was found to be a significant influence on behaviours in the empirical literature, however was not identified as important by women during the FGDs, so was removed.

An attribute representing whether a client was drunk was identified during these seminars as being a proxy factor for assessing a client's risk profile, and for the draft task client regularity and perceived risk were both included. To minimise complexity, we initially opted to frame the task around a vaginal sex act, however later changed this as a result of comments from piloting.

Figure 4: Draft choice task initially presented to sex worker community advisory board

	Act A	Act B
Price	 50 Rand	 200 Rand
Condom	 Male Condom	 No Condom
Client Type	<div>New Client</div> New Client	<div>New Client</div> New Client
Client Risk	 Client looks risky	 Client does not look risky

This draft task in Figure 4 was presented to the twelve-person sex worker community advisory board of Wits RHI in October 2015 who advised that all attributes were meaningful and relevant to the choice task. One round of piloting took place with a sample of ten peer-educators at Wits RHI working in central Johannesburg and were part of a population which was not in the final sampling frame.

This piloting process led to a substantial reshaping of the DCE. The price and condom attributes remained, however client type was identified by many pilot participants as unimportant relative to the other attributes – this was reinforced by analysis of this pilot data. Instead, participants unanimously recommended focusing on the type of sex being supplied – vaginal or anal – which would have a much greater bearing on decision making. This also allowed analysis to be broadened to estimate a price differential for different types of sex, as in evidence suggesting that different types of commercial sex commanded different prices, with anal sex consistently selling for a greater price than vaginal sex[40, 45]. Both choice task framings – current practice and HIV protection under PrEP use – was thought to be very clear, and was not changed.

The client risk attribute also received attention during piloting, and the meaning of “risk” was considered ambiguous by participants. Through discussion with pilot participants and re-examination of FGD data, we opted to a) limit the description of risk to exposure to HIV or STIs, and not the potential of violence from clients, and b) separate HIV and STI risk. Participants reported the differing consequences of STI and HIV infection, where STI acquisition was perceived as a small health impact but a large potential to negatively affect earnings in the short-medium term, whilst HIV infection was perceived a larger longer-term risk, with negative implications occurring after women aimed to leave sex work[43].

Time pressure to complete data collection, particularly with the uncertainty over the length of time required to reach sample size through the RDS process used in FSW data

collection, meant that a full second round of piloting with the revised task was not possible. Instead, the final task design and appearance was tested individually with five of the pilot participants. Participants reported that the explicit representation of STI risk was very clear, whilst interviewers reported throughout the survey that the slightly humorous nature of this attribute worked to relax participants, and break down the barrier between interviewer and respondent.

Final input on the appearance of the FSW DCE was obtained from fieldworkers during their training. The only change at this stage was the representation of a client who was not perceived to have HIV, where a green ribbon was used in contrast to the red AIDS ribbon, which is widely used in South Africa to denote AIDS-related issues. Although meaningless outside of the context of this study, this representation of the absence of HIV risk was reported by interviewers to be particularly clear to explain, and resonated among respondents. The final presentation of the task is shown in Figure 5.

Figure 5: Example of final choice task (without HIV protection framing)

ODK Collect > Final_DCE_survey

You have the choice between providing services to two clients. Which would you prefer?

	Client A	Client B	Neither
2 of 10	 Male or Female Condom	 No Condom	Would not provide services to either client
Condom	 Anal sex	 Vaginal sex	
Sex	 You don't think this client has HIV	 You think this client has HIV	
HIV Risk	 You think this client has an STI	 You don't think this client has an STI	
STI Risk	 50 Rand	 400 Rand	
Price			

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Chapter 6: Paper R1 – Divergent preferences for HIV prevention: A discrete choice experiment for multipurpose HIV prevention products in South Africa

Overview of paper R1

As identified in chapter 1, the development of candidate MPT products offers optimism for increased coverage of HIV prevention in general and high-risk populations. This paper describes the design, implementation, and results of a DCE assessing preferences for five new products among four population groups: adult men and women in the general population (aged 18-49), adolescent girls (aged 16-17), and self-identifying female sex workers (aged 18-49).

This work undertaken in this thesis was reviewed and approved by the Human Research Ethics Committee (HREC) at the University of the Witwatersrand, and the Research Ethics Committee at LSHTM. Approval letters from these committees are presented in Appendix IV. Full informed consent was obtained from all participants during qualitative and quantitative data collection. Appendix VI contains the information sheets and informed consent forms used in this process, Appendix VII presents the FGD discussion guide, and Appendix VIII the information given to participants on the new HIV prevention products shown to them.

Appendix IX contains a paper, published in 2016 in *BMJ Open*, describing the development of this DCE, and gives additional information on data collection methods over and above that detailed in this chapter.

Data were analysed using multinomial (MNL), latent class (LC) and mixed multinomial logit (MMNL) models. As noted in the paper, although commonly applied in choice modelling, the MNL requires restrictive assumptions of the underlying preferences of respondents – notably, that every individual in the population has identical preferences.

This assumption is relaxed by the use of a semi-parametric LC model to separate respondents into different groups based on similarity of preferences, with group membership predicted by observable characteristics. The MMNL model is also used, which allows preferences to vary across individual, incorporating taste heterogeneity through the introduction of random parameters.

The paper is presented as accepted to the journal *Medical Decision Making* in July 2017, including the superscript referencing style. Permission to include in this thesis was not obtained before submission, so the accepted version is presented here. A supplementary section immediately following the paper details an additional analysis using observable characteristics as interaction terms in a MNL model, which was not included in the final paper.

This paper fulfils research objective 1 to quantify the determinants of demand for new HIV prevention technologies among adult men, women, and adolescent girls in the general population, and female sex workers. The results are also used to predict product uptake in the cost-effectiveness model in paper R2, so therefore also contribute to objective 2.



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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Matthew Quaife
Principal Supervisor	Fern Terris-Prestholt
Thesis Title	Using stated preferences to estimate the impact of new HIV prevention products in South Africa

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Medical Decision making
When was the work published?	2017
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	
Have you retained the copyright for the work?*	No - non-formatted version
Was the work subject to academic peer review?	

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	led design + analysis, wrote first draft, incorporated co-author comments
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Student Signature: _____

Date: 17/7/17

Supervisor Signature: _____

Date: 17/7/17

Divergent preferences for HIV prevention: A discrete choice experiment for multipurpose HIV prevention products in South Africa

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Keywords: HIV prevention, discrete choice experiments, pre-exposure prophylaxis, key populations, South Africa

Abstract: The development of antiretroviral (ARV)-based prevention products has the potential to substantially change the HIV prevention landscape, yet little is known about how appealing these products will be - compared to existing options - outside of clinical trials. We conducted a discrete choice experiment (DCE) to measure preferences for five new products among four important populations in the HIV response: adult men and women in the general population (aged 18-49), adolescent girls (aged 16-17), and self-identifying female sex workers (aged 18-49). We interviewed 661 self-reported HIV negative participants in peri-urban South Africa, who were asked to choose between three unique, hypothetical products over ten choice sets. Data were analysed using multinomial, latent class and mixed multinomial logit models. HIV protection was the most important attribute to respondents; however, results indicate significant demand among all groups for multipurpose prevention products which offer protection from HIV infection, other STIs, and unwanted pregnancy. All groups demonstrated a strong preference for long-lasting injectable products. There was substantial heterogeneity in preferences within and across population groups. These results suggest that stimulating demand for new HIV prevention products may require a more nuanced approach than simply developing highly effective products. No one product is likely to be equally attractive or acceptable across different groups. This study strengthens the call for effective and attractive multipurpose prevention products to be deployed as part of a comprehensive combination prevention strategy.

Ethical Statement: The study was reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee (M140614) and the Research Ethics Committee at the London School of Hygiene and Tropical Medicine (8541-2). All participation in the DCE and supporting qualitative studies was voluntary and subject to completion of a written informed consent process. Adolescent participants were asked for written assent, in addition to written consent provided by a parent or guardian per South African law. A comprehensive distress protocol adopted as standard study

procedure ensured that participants who answered in the affirmative to questions about violence and/or other potentially distressing situations were referred to named persons at local clinics and NGOs for additional support.

Funding Sources: Fieldwork was supported by the Bill and Melinda Gates Foundation. MQ receives an Economic and Social Research Council 1+3 studentship. Support for the analysis of this project is made possible by the generous support of the American people through the United States Agency for International Development (USAID) under the terms of the HealthTech V Cooperative Agreement #AID-OAA-A-11-00051. The contents are the responsibility of LSHTM and PATH and do not necessarily reflect the views of USAID or the US Government.

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Author Contributions: Conceived, designed and tested the DCE: MQ RE MC PV SDM FTP. Led fieldwork: MQ MC. Analysed the data: MQ FTP PV. Wrote and revised the manuscript: MQ RE MC PV MKB MM SDM FTP.

Introduction

South Africa has the largest HIV epidemic in the world, but the health and economic burden of HIV infection is not borne equally.¹ Women are 40% more likely to be living with HIV than men, whilst adolescent girls (aged 15-19 years) face an 80% cumulative lifetime risk of HIV acquisition.^{2, 3} Female sex workers (FSW) are designated as a key population for HIV treatment and prevention and estimates suggest that the HIV prevalence among this group in Johannesburg is 72%.⁴

Recent technological developments have led to a number of candidate products for antiretroviral (ARV)-based HIV prevention.⁵ Yet before these are introduced, it is important to understand who will use them to reliably estimate their impact and best plan their introduction. Where different population groups have different preferences for products it is critical that this heterogeneity is identified to ensure that relevant products are made available to potential users. Even if only a small proportion of the population only uses products, they may still be cost-effective if used consistently and effectively among those at risk of HIV acquisition. ARV-based pre-exposure prophylaxis (PrEP) has been shown to offer varying degrees of protection to HIV negative persons when delivered via daily or intermittent oral tablet^{6, 7} or long-lasting intravaginal ring^{8, 9}. However, product protection has been variable during clinical trials as microbicide gels and vaginal rings were found to confer substantially less protection to younger users than to older women primarily due to adherence issues.^{8, 10} This is particularly concerning as adolescent girls and young women (AGYW) face a far greater risk of HIV acquisition than older women, or men of any age.^{3, 10}

A promising field in HIV prevention is the development of multipurpose technologies (MPTs), products which simultaneously provide protection from two or more of HIV, other STIs, and unintended pregnancy.^{11, 12} Current MPTs in development include: (1) long-acting drug delivery systems such as intravaginal rings designed to protect from

HIV infection and pregnancy (currently in a phase-I trial, ClinicalTrials.gov Identifier: NCT02235662); (2) pericoital drug delivery systems such as vaginal gel, tablets and films designed to protect from HIV; and (3) a combination of products such as a contraceptive diaphragm used with microbicide gel designed to protect from HIV, STIs and pregnancy.^{11, 13} Although MPT development is likely to be costly and complex, their benefits may also be large. Firstly, products offering more than one indication may be more attractive to potential users than single-purpose products. Secondly, MPT use could *crowd-in* protection from lesser valued attributes. For example, where users value contraceptive properties more than they do HIV prevention, additional HIV protection would be a positive externality from the use of a dual-protective product. Thirdly, the multipurpose nature of MPTs may reduce the stigma of accessing HIV prevention tools, which has been shown to be a substantive barrier to use, and prevent products from being perceived as for certain populations only.^{14, 15}

Accounting for the perspectives of end-users in product formulation and delivery could lead to more attractive products, greater uptake and adherence, and increased population protection. This study uses a discrete choice experiment (DCE) to elicit the preferences for five HIV prevention products (oral PrEP, a microbicide gel, a SILCS diaphragm used in concert with gel, an intravaginal ring, and an injectable) from four population groups (adult men and women aged 18-49, adolescent girls aged 16-17 and self-identifying female sex workers aged 18-49) in Vosloorus, a township in peri-urban Ekurhuleni, around 30km from Johannesburg in the Gauteng province of South Africa. Because there are no observed data for many of these products, we gathered primary stated preference data using the DCE, an end-user focused approach to identifying key determinants of demand.^{16, 17} DCEs ask respondents to choose their preferred product or service from a set of alternatives over a number (usually between 8-10) of choice tasks. By looking at how respondents choose across repeated scenarios allows researchers to quantitatively elicit the key drivers of decision making.¹⁸ Although men

who have sex with men (MSM) are a high-risk group in South Africa, they were not purposively sampled in this study a) because the contraceptive indication of interest would have little relevance among MSM practicing solely same-sex intercourse, b) the stigma associated with same-sex activity was considered to place interviewers or participants at risk, and c) the small number of MSM likely to be in the geographical location of the survey coupled with the intensive resources required to reach adolescent and FSW groups. Where a small number of MSM were identified the household survey, they were not excluded from data collection or analysis based on reported same-sex activity.

Already popular in the health literature¹⁹, DCEs are being increasingly applied in the HIV and sexual health fields. Previous work conducted in South Africa found HIV prevention efficacy to be a key driver of demand for a microbicide, a diaphragm or female condom.²⁰ A DCE was used to indicate that a rectal microbicide was acceptable among MSM in Thailand, with male sex workers more likely to use an efficacious product than other men.²¹ A DCE in Tanzania showed that different population groups had markedly different preferences for HIV testing interventions among respondents who had been tested previously.²² Two DCEs in Malawi found heterogeneity in the preferences of young people for HIV, sexual health, and family planning services.^{23, 24} Finally, a conjoint analysis in seven countries found PrEP to be broadly acceptable to potential end-users.²⁵

To our knowledge, this is the first study to explore how preferences for new HIV prevention products vary across general and key population groups, and provides important information on a) preferences among different groups, b) variation in preferences within groups, and c) whether new products will be used alongside or instead of condoms. Such “condom substitution” has been a concern in the design of PrEP programmes and demonstration projects, yet evidence is mixed as to whether condomless sex will increase after PrEP introduction.^{6, 26-28}

Methods

Study context

Primary data collection was carried out in the town of Vosloorus, around 30km south-east of Johannesburg, South Africa. Vosloorus contains a broad range of residential contexts representing a range of demographic, socioeconomic and cultural characteristics. Formative research took place between August and September 2015, and the survey ran from October to December 2015. Further details on study context and methods have been published in the study protocol^{29 3} and no changes were made to the study design or analysis plan.

Development and design of the discrete choice experiment

The DCE was developed through an analysis of a previous DCE and focus groups discussions carried out in previous research^{18, 21}, specifically identifying important characteristics of prevention products and exploring optimal ways to present these in a clear and relatable manner to participants. This was supplemented by a scoping literature review to identify new products and additional attributes which could be important to respondents, which was added to and refined through piloting. We opted to show three alternatives of new products in each task using an unlabelled design where each alternatives represent a generic product within which all characteristics can change as prescribed by the statistical design. Though an unlabelled design, where each alternative represents a fixed product category, would have led to greater statistical efficiency, feedback from piloting was that a choice task with five labelled alternatives plus an opt-out was too complex. The opt-out alternative displayed characteristics of a male condom or non-protection, depending on what the respondent reported using in their last sex act.

³ Chapter 7 of this thesis






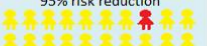

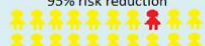








The DCE was pre-piloted among 17 respondents from across the target populations. A separate design was generated for male and female groups as men can only initiate use of two of the five potential products (the injectable and oral PrEP). The full survey and DCE was then piloted among 45 respondents from the target sampling frame. Few changes were made to the DCE after piloting, except to the side-effects attribute where minor and frequent side-effect symptoms of nausea, stomach cramps, and dizziness were included over major, less frequent side-effects such as reduction in bone mineral density or liver toxicity. This is a limitation of this study, but was necessary due to difficulties in participant comprehension of a) varying probabilities of side-effects and b) medical implications of more serious conditions in a brief DCE interview. Priors from analysis of pilot data (n=17) were used in NGENE software³⁰ to generate a single D-efficient design with ten tasks, which avoided dominated or duplicated alternatives as recommended³¹. A D-efficient design was chosen with the aim of improving precision in final model estimates whilst accounting for design constraints arising from restrictions on the frequency that products could be used. The final six attributes of the DCE and their levels are shown in Table 1, and Figure 1 shows an example of how choice tasks were presented to respondents who reported using a condom in their last sex-act. For participants who reported not using a condom at last sex, the final column showed a “nothing” alternative, whilst male respondents saw identical side-effects images but with male characters. The final design incorporated ten choice tasks, with one additional task a repeat to check the consistency of responses.

Table 1: Attributes and levels

Attribute	Levels
Product	Oral pre-exposure prophylaxis, Microbicide gel, Microbicide gel with SILCS diaphragm, Vaginal ring, Injectable pre-exposure prophylaxis
HIV protection	55%, 75%, 95%
Pregnancy prevention	Prevents pregnancy, Does not prevent pregnancy
Frequency of use ⁴	Every time you have sex, Once per day, Once per week, Once per month, Once per three months, Once per six months, Once per year
Protection against other STIs	Protects against other STIs, Does not protect against other STIs
Side-effects (probability of occurrence fixed)	Stomach cramps/pain, Nausea/feeling sick, Dizziness, None

Figure 1: Example of DCE task as shown to a female who used a condom at last sex

Here are the products and this is what they do. Please select the product you would most prefer.

10	A	B	C	Condom
Product	Oral PrEP 	Vaginal ring 	Microbicide Gel 	Condom 
HIV Protection	55% risk reduction  11 of 20 people remain HIV negative	95% risk reduction  19 of 20 people remain HIV negative	55% risk reduction  11 of 20 people remain HIV negative	95% risk reduction  19 of 20 people remain HIV negative
Pregnancy Protection	Prevents pregnancy 	Does not prevent pregnancy 	Prevents pregnancy 	Prevents pregnancy 
Frequency	365 times per year (daily)	4 times per year	365 times per year (daily)	Every sex
STI protection	STI Protection Prevents STIs	STI Protection Does not prevent STIs	STI Protection Prevents STIs	STI Protection Prevents STIs
Side Effects	 No Side Effects	 Nausea/feeling sick	 No Side Effects	 No Side Effects

⁴ Because no product can be used at all frequencies, the design contained constraint terms where only relevant frequencies were presented alongside products. Frequencies were chosen to be informative for product development: Oral PrEP – Daily, weekly, monthly; Microbicide Gel – coitally; SILCS diaphragm and microbicide gel – coitally, daily; Vaginal ring – weekly, monthly, three monthly, six monthly; Injection – three monthly, six monthly, annually

Survey methods

A household survey sampled adult men and women (aged 18-49), and adolescent girls (aged 16-17) randomly. Clusters of dwellings (census enumeration areas) within Ekurhuleni were selected at random using municipal data and aerial photographs, and interviewers contacted every second property after a random start. All eligible participants were interviewed within selected households. The DCE and background survey was administered in English, Zulu and Khosa languages using Open Data Kit (<https://opendatakit.org>) software on tablet computers, and participants were given ZAR 50 (GBP £2.50) vouchers as compensation for their time. A team of twelve experienced interviewers from a specialist local data collection firm, Progressus Research and Development (<http://www.progressus.co.za>) implemented the survey.

FSWs are a hard to reach population and we used respondent-driven sampling (RDS) to sample 203 active FSW participants.³² Peer educators, most of whom were practicing sex workers, were used to locate 'hotspots' in Ekurhuleni. First, 12 were asked to act as 'seeds' to start RDS chains in different areas (i.e. women working in brothels, hotels or on the street). Seeds were invited to complete the survey and received the same ZAR 50 (GBP £2.50) compensation as participants in the general population. Women were then given four coupons containing study information to distribute to colleagues. When each referred colleague attended for interview, their recruiter received a small incentive in the form of a ZAR 20 (GBP £1) voucher.

Choice Modelling

We model choices using random utility models, choosing this approach over alternative methods (random regret minimisation for example) due to its proven consistency in explaining choice behaviour in health applications. We assume that individual $i(i=1,...,N)$ makes choices such that they maximise utility over the four alternatives presented ($j=1,2,3,4$). Their axiomatic utility function U_{ij} is decomposed into an

explainable systematic component V_{ij} and a random component ε_{ij} , and we specify an indirect utility function for the utility of respondent i from choice j in choice set c as the linear combination of attributes and an error term:

$$V_{ijc} = X_{ijc}\beta + \varepsilon_{ijc} \quad (1)$$

With V_{ijc} the utility derived from a choice, $X'_{ijc}\beta$ the component of utility that is captured by DCE attributes, and ε_{ijc} a stochastic (random) component of utility. We specify the vector X_{ijc} as the set of product attributes:

$$X_{ijc}\beta_j = \beta_0 + \beta_1 Product_j + \beta_2 HIV_j + \beta_3 Contraception_j + \beta_4 STI_j + \beta_5 Frequency_j + \beta_6 SideEffects_j \quad (2)$$

Where $Product_j$, HIV_j , $Contraception_j$, STI_j , $Frequency_j$, and $SideEffects_j$ are the design attributes of the DCE, and β_0 a constant. We first estimate equation (1) using a multinomial (or conditional) logit model (MNL) which estimates the probability of individual i choosing alternative j among the set of options c as a probabilistic function of design attributes:

$$P_{ijc} = \frac{\exp(X_{ijc}\beta)}{\sum_j \exp(X_{ijc}\beta)} \quad (3)$$

Although described as the workhorse of discrete choice modelling, the MNL requires two restrictive assumptions: the IIA assumption of independence of irrelevant alternatives (concordant with the IID distribution of the disturbance), and homogenous preferences across individuals where every individual is assumed to have the same tastes as the sample average, which does not allow us to uncover differences in preferences that are important in guiding policy.¹⁸ We assume that individuals choose the service associated

with the highest utility such that the probability that individual i chooses alternative j over k is given as:

$$\Pr_{ji} = \Pr(U_{ji} > U_{ki}) = \Pr(V_{ji} + \varepsilon_{ji} > V_{ki} + \varepsilon_{ki}) = \Pr(V_{ji} - V_{ki} > \varepsilon_{ki} - \varepsilon_{ji}) \quad (4)$$

In this paper, as different MNL models are estimated for each population, the assumption required is homogeneity of preferences within each group. As groups are more homogenous in nature due to separate inclusion criteria, assuming identical preferences across members within each group may be less restrictive than assuming this across the range of populations in our sample.

Nevertheless, to recognise that individuals within groups may have different preferences, we apply a random parameter logit (MMNL or mixed logit random parameter) model. The MMNL allows for preference (taste) heterogeneity within groups so does not require the IIA assumption to hold. Briefly, the MMNL extends the MNL model by decomposing the error term into two components:

$$U_{ij} = V_{ij} + [\Gamma_{ij} + \varepsilon_{ij}] \quad (5)$$

Which, when the distribution of the random component Γ_{ij} is specified by the analyst, is used to estimate individual-level coefficients:

$$\beta_{ik} = \beta_k + \delta_k Z_i + \Gamma_k v_{ik} \quad (6)$$

Where $\delta_k Z$ reflects observable heterogeneity, and $\Gamma_k v_{ik}$ unobservable heterogeneity.

Finally, we use a latent class approach to explore unobserved heterogeneity in choice data. A semi-parametric approach, a latent class model assumes the existence of underlying subgroups (classes) of respondents whose membership of each class is characterised by unobserved, or latent, variables. A posterior probability is assigned to each participant for membership to each class, and when participants are allocated to

classes based on their highest probability it is possible to compare the observable characteristics of participants across classes ^{18, 34}.

Latent class modelling offers a different approach to relaxing the IIA assumption of the MNL model. Furthermore the basic latent class model does not require parametric distributional assumptions to be imposed by the analyst, whilst results have been shown less sensitive to computational variations in estimation, such as starting values or optimisation algorithms which can vary across software packages.^{35, 36} A latent class approach estimates separate parameter vectors for different classes of the sample with MNL models. The model relaxes the IIA assumption by assuming that preferences are homogenous within, but not across, classes. Thus the probability of respondent i choosing alternative j in choice set c conditional on class membership k is:

$$P_{ic}(j|\beta_k) = \sum_{k=1}^K \pi_{ik} \frac{\exp(X_{ijc}\beta_k)}{\sum_j \exp(X_{ijc}\beta_k)} \quad (7)$$

The probability of respondent i belonging to class k is π_{ik} . Class membership is unobservable, however, we can regress the probability of class membership on a set of observable characteristics such that:

$$\pi_{ik} = \frac{\exp(Z_i'\delta_k)}{\sum_{k=1}^K \exp(Z_i'\delta_k)} \quad (8)$$

With Z_i a vector of individual characteristics, and δ_k a vector of parameters to be estimated.

We run latent class logit models on the male sample, alongside a pooled sample of all three female groups. This approach removes the implicit assumption that women's preferences will differ by their sample category, and instead allows the data to drive evidence of variation and similarity among subgroups. By pooling we lose generalisability from the results of this specification; however, results from the pooled

analysis are useful to identify important subgroups of the female population. We assess the optimal number of classes through comparison of model fit via log-likelihood function and Akaike Information Criteria (AIC).

Heterogeneity

We use two approaches to explore heterogeneity in preferences. First, we examine the distribution parameters of the MMNL model to see where variation remains in addition to that captured by the random parameters. Secondly, we estimate the latent class model (equation 8) and explore how preferences vary by class, specifying several observable characteristics which influence the probability of class membership.

Our rationale for including these observable characteristics is as follows. Age is strongly associated with HIV and pregnancy risk^{37,38}, yet little is known about the effect of age on preferences for protection against HIV or pregnancy. Structural drivers are legal, economic and social factors which shape HIV risk.³⁹ Exposure to intimate partner violence (IPV) has been shown to be associated with increased HIV risk in many contexts^{40, 41}, whilst limited livelihood opportunities, and unrestricted alcohol availability alongside drinking norms are also significant factors in HIV risk.⁴²⁻⁴⁵ Finally, life circumstances play an important role in the extent to which people place themselves at, or are able to protect themselves from, HIV risk.^{46, 47} We therefore explore attitudes towards pregnancy among women and how preferences may be affected by male circumcision, which reduces the likelihood of a male acquiring HIV.^{48, 49} Finally, we explore associations with protective attributes, having an external partner in the previous three months, and having high HIV knowledge as assessed by the number of correct answers on a knowledge tool.⁵⁰

Model estimation

Models were estimated in NLOGIT 5⁵¹ through a maximum likelihood approach and MMNL models were estimated using 500 Halton draws with start values obtained from

a MNL model. All parameters were generic across three unlabelled alternatives, with labels entering the DCE through an attribute level. All design attributes were specified as random with parameters following a normal distribution to characterise our uncertainty in the nature and direction of heterogeneity around coefficients. Triangular and lognormal distributions were tested and did not change the sign or significance of the main effects. General population samples were analysed with survey weighting such that age and sex characteristics matched those of the general population. FSW RDS data were weighted using age characteristics using RDSAT software.⁵² All attribute levels were effects coded⁵, except for HIV protection which was estimated linearly.⁵³

Results

Sample characteristics and generalisability

In the household survey, of 2271 persons identified door-to-door, 650 were eligible (29%). Of those, 30 (5%) were not found after five attempts and 11 (2%) refused to be interviewed, leading to 609 (94%) completed interviews. In total 661 interviewees met the DCE eligibility criteria across the four populations. Notably, 126 (62%) of adolescent girls reported not being sexually active whilst self-reported HIV prevalence was broadly comparable across and within populations to that of other representative surveys.^{3,4} The inclusion criteria for adolescent girls did not require sexual activity because adolescent girls face substantial and immediate risk of HIV at sexual debut, whilst HIV prevention programmes do not target based on reported sexual activity. The preferences of non-sexually active adolescent are important for ensuring that attractive products are made available at the earliest possible exposure to HIV risk. In addition, if sexual activity was an explicit inclusion criterion for adolescents, confidentiality could have been breached if other members of the household knew that an interview did, or did not, take place.

⁵ Effects coding is similar to dummy coding in that it allows for non-linear effects in attribute levels, but does not perfectly confound the base attribute level with the grand mean of the utility function. Coefficients are therefore interpreted as divergence from the mean for that attribute

Table 2: Descriptive statistics for DCE respondents by population

	Adult Males	Adult Females	Adolescent Girls	Female Sex Workers
Participation				
Recruited for survey	202	203	204	203
HIV positive	16 (8%)	35 (17%)	5 (2%)	81 (40%)
Not sexually active	4 (2%)	10 (5%)	-	0
Eligible and completed DCE	182 (90%)	158 (78%)	199 (98%)	122 (60%)
Socio-demographic variables	N (%), Mean (SD)	N (%), Mean (SD)	N (%), Mean (SD)	N (%), Mean (SD)
Age	29 (7.6)	29 (7.83)	17 (0.49)	31 (6.17)
Education: Primary or less	18 (12%)	29 (16%)	51 (28%)	36 (20%)
Finished secondary	127 (70%)	1234 (68%)	129 (71%)	138 (76%)
College or higher	33 (18%)	29 (16%)	2 (1%)	5 (3%)
Employment: Full time	58 (32%)	38 (21%)	0 (0%)	66 (36%)
Part time	36 (20%)	35 (19%)	4 (2%)	29 (16%)
Student/scholar	24 (13%)	27 (15%)	164 (90%)	0 (0%)
Work seeker/unemployed	47 (26%)	71 (39%)	13 (7%)	40 (22%)
Other	15 (8%)	11 (6%)	0 (0%)	46 (25%)
In a stable relationship	131 (72%)	157 (86%)	160 (88%)	118 (65%)
Cohabiting	40 (22%)	53 (29%)	0 (0%)	29 (16%)
Household monthly income:				
<R5,000	133 (73%)	127 (70%)	113 (62%)	113 (62%)
R5,000-15,000	42 (23%)	40 (22%)	60 (33%)	55 (30%)
R15,000+	5 (3%)	7 (4%)	7 (4%)	15 (8%)
Sexual history variables				
Age at first sex	16.55 (3.4)	17.88 (1.98)	15.68 (1.09)	17.96 (2.57)
Number of lifetime partners	13.06 (25.94)	4.55 (3.53)	2.14 (1.69)	1626.54 (2185.95)
Number of partners in previous year	2.51 (4.45)	1.24 (1.49)	1.34 (0.85)	462.83 (556.59)
Current regular sexual partner	131 (72%)	157 (86%)	160 (88%)	118 (65%)
Condom use at last sex with regular partner	124 (68%)	78 (43%)	118 (65%)	166 (91%)
Currently using any form of contraception	140 (77%)	126 (69%)	149 (82%)	149 (82%)
Ever received an HIV test	131 (72%)	157 (86%)	160 (88%)	118 (65%)
External sexual partner in prior 3 months	36 (20%)	9 (5%)	9 (5%)	166 (91%)
Circumcised	118 (65%)			

Nb. Values of continuous variables italicised

Table 2 displays the descriptive statistics for eligible respondents in each population. Comparability is limited across groups due to varying inclusion criteria for adolescent girls and FSWs, the latter also sampled through RDS. The mean age across adult groups was similar and whilst a large number of respondents in each group reported being in a relationship, many fewer reported cohabiting with a sexual partner. Reported lifetime sexual partners among adult males (13.06) were higher than among adult females (4.55). Reported condom use at last sex with a regular partner was significantly lower among adult females (43%) than any other group, though this Figure is comparable with that of 34% from a nationally representative survey.^{3, 4}

The DCE was well understood by participants; just 2% of respondents reported finding the DCE quite difficult or very difficult, whilst 81% of respondents chose the same alternative twice in the repeated choice task. 61% of respondents chose the product (or one of the products when values were duplicated) with the highest HIV protection in every choice set.

Analysis of preference data

Table 3 shows MMNL results and reports the coefficients of each attribute level parameter. Results from the MNL model are given in supplementary Table 2.

Table 3: MMNL main effects results

	Adult Males Coeff. (SE)	Adult Females Coeff. (SE)	Adolescent Girls Coeff. (SE)	FSW Coeff. (SE)
Products: Oral PrEP	-2.52 (1.284)**	-0.45 (0.15)***	-0.31 (0.11)***	-1.09 (0.169)***
Microbicide Gel	-	-0.29 (0.19)	-0.17 (0.14)	-1.03 (0.21)***
Vaginal Ring	-	-0.23 (0.15)	-0.16 (0.11)	-0.13 (0.149)
SILCS Diaphragm	-	-0.23 (0.28)	-0.16 (0.27)	-0.28 (0.265)
Injectable	2.52 (1.284)**	1.21 (0.28)***	0.8 (0.28)***	2.52 (0.35)***
Protection: HIV protection (100%)	5.32 (1.650)***	3.14 (0.77)***	2.33 (0.53)***	2.78 (0.694)***
Pregnancy prevention	0.16 (0.066)**	0.34 (0.08)***	0.16 (0.05)***	0.43 (0.087)***
STI protection	0.75 (0.211)***	0.41 (0.1)***	0.22 (0.06)***	1.04 (0.105)***
Frequency of use: Daily	-6.91 (0.227)	0.32 (0.16)	0.17 (0.16)	0.3 (0.213)
Coitally	-	0.13 (0.29)*	0.14 (0.23)	0.25 (0.281)
Weekly	3.77 (2.207)*	0.29 (0.17)**	0.15 (0.13)	0 (0.173)
Monthly	-0.89 (1.913)	0.4 (0.16)	0.4 (0.12)***	0.52 (0.155)***
Every 3 months	-1.16 (1.825)	0.26 (0.17)	0.06 (0.13)	-0.02 (0.181)
Every 6 months	4.14 (2.32)*	0.14 (0.2)	0.01 (0.15)	0.23 (0.177)
Annually	1.06 (2.164)	-1.53 (0.5)***	-0.93 (0.45)	-1.28 (0.453)***
Side-effects: Dizziness	2.42 (2.318)	-0.16 (0.07)*	-0.13 (0.07)*	-0.37 (0.108)**
Stomach cramps	-1.98 (-1.291)	0.09 (0.11)	0.07 (0.08)	0.09 (0.127)
Nausea	-4.19 (-2.277)*	-0.06 (0.1)	0.02 (0.08)	0.16 (0.103)
No side-effects	5.06 (1.792)***	0.13 (0.08)	0.05 (0.09)	0.11 (0.093)
Opt out	42.2 (14.783)***	3.01 (0.65)***	2.05 (0.4)***	1.2 (0.598)**
Male condom (opt out)	1.34 (1.275)	2.77 (0.59)***	0.6 (0.09)***	2.86 (0.32)***
Distribution parameters				
Oral PrEP	14.06 (4.661)***	0.81 (0.13)***	3.77 (5.14)	1.51 (0.13)***
Microbicide Gel	-	0.79 (0.14)***	11.4 (6.37)*	1.08 (0.179)***
Vaginal Ring	-	0.38 (0.19)**	3.06 (5.28)	0.47 (0.102)***
Injectable	14.06 (4.661)***	0.36 (0.09)***	36.42 (8.69)***	1.39 (0.146)***
SILCS Diaphragm	-	0.92 (0.16)***	7.29 (2.37)***	0.73 (0.237)***
HIV protection (100%)	0.28 (0.094)***	0.04 (0.01)***	0.17 (0.07)***	0.05 (0.003)***
Pregnancy protection	2.58 (2.966)	0.42 (0.07)***	3.23 (2.78)	0.76 (0.07)***
STI protection	10.85 (3.953)***	0.89 (0.09)***	21.58 (5.18)***	1.16 (0.085)***
Daily	10.67 (10.617)	0.3 (0.53)	1.12 (8.21)	1.24 (0.153)***
Coitally	-	0.19 (0.63)	0.19 (6.26)	1.64 (0.216)***
Weekly	2.81 (4.202)	0.01 (0.12)	17.7 (7.6)**	0.09 (0.157)
Monthly	0.77 (4.73)	0.12 (0.2)	15.56 (7.07)**	0.13 (0.113)
Every 3 months	2.99 (4.446)	0.43 (0.14)***	34.98 (10.49)***	0.66 (0.185)***
Every 6 months	2.22 (4.935)	0 (0.17)	14.26 (6.73)**	0.26 (0.194)
Annually	21.4 (7.74)***	0.15 (0.27)	1.01 (0.2)***	1.01 (0.199)***
Dizziness	0.96 (0.342)	0.54 (0.34)	5.15 (6.84)	0.42 (0.075)***
Stomach cramps	0.32 (3.121)	0.15 (0.16)	7.56 (4.07)*	0.6 (0.11)***
Nausea	2.38 (3.795)	0.05 (0.17)	23.01 (6.61)***	0.01 (0.108)
Opt out: No side-effects	2.09 (2.943)	0.17 (0.13)	0.28 (0.08)***	0.28 (0.083)***
Male condom (opt out)	29.9 (9.716)***	2.97 (0.44)***	30.9 (8.58)***	0.62 (0.138)***
Log-likelihood	-2041.3	-1758.92	-2107.8	-2457.68
AIC	4136.7	3585.9	4251.7	4985.4

***, **, * ==> Significance at 1%, 5%, 10% level. Models for each population analysed separately, and indicated as significant if different from zero.

Where coefficients are significantly greater than zero, an attribute can be interpreted as having a relatively positive impact on participant utility. The magnitude of coefficients can be directly compared within each model. The significance of coefficients (i.e. what is important to people's choices) can be compared across populations, but due to possible differences in the scale of choice data across groups, coefficients cannot be directly compared across populations. In both specifications and across all groups HIV protection was the strongest determinant of choice, whilst protection against pregnancy and other STIs was also significantly attractive. The absence of side-effects was important to adult men but not to any female groups, although FSWs found nausea significantly worse than other side-effects. There was no clear pattern of demand around frequency of use across groups.

There are some differences between the product coefficients in the MNL and MMNL models, indicating that tastes vary within populations – this is also highlighted by the positive distribution parameters. In both specifications adult women and FSWs significantly dislike oral PrEP and favour injectable products, with FSWs additionally disliking microbicide gels. Among adolescent girls, the MNL indicates a significant dislike for the vaginal ring which is insignificant in the MMNL model, whilst the MMNL model shows the same pattern of statistically significant preferences for oral PrEP and injectable products as other female groups.

Preference Heterogeneity

Latent class specification

Latent class models are presented for female and male respondents in panels A and B of Table 4 respectively, and were computed without survey weighting.

Table 4: Latent class logit: Pooled samples

	Panel A: All females (adult women, adolescent girls, FSWs)			Panel B: All males	
	Class 1 34% of sample Coeff. (SE)	Class 2 19% of sample Coeff. (SE)	Class 3 48% of sample Coeff. (SE)	Class 1 42% of sample Coeff. (SE)	Class 2 58% of sample Coeff. (SE)
Products: Oral PrEP	0.12 (0.31)	-0.14 (0.23)	-0.04 (0.1)	0.37 (0.19)*	-0.04 (0.1)
Microbicide Gel	0.01 (0.32)	0.02 (0.38)	0.05 (0.14)	-	-
Vaginal Ring	-0.27 (0.34)	-0.37 (0.25)	-0.21 (0.11)*	-	-
SILCS Diaphragm	-0.15	-0.18	0.21	-	-
Injectable	0.28 (0.69)	-0.24 (0.67)	0.01 (0.31)	-0.37	0.04
Protection: HIV protection (100%)	0.53 (1.79)	7.59 (1.05)***	3.28 (0.64)***	5.79 (1.45)***	3.44 (0.64)***
Pregnancy prevention	1.33 (0.19)***	0.27 (0.12)**	0.26 (0.06)***	0.37 (0.11)***	-0.02 (0.06)
STI protection	1.34 (0.21)***	0.21 (0.13)	0.29 (0.06)***	0.48 (0.11)***	0.51 (0.07)***
Frequency of use: Daily	-0.45 (0.52)	-0.5 (0.35)	-0.15 (0.17)	0.48 (0.34)	-0.22 (0.16)
Coitally	0.28 (0.56)	-1.06 (0.54)**	-0.22 (0.24)	-	-
Weekly	-0.65 (0.42)	0.03 (0.31)	-0.21 (0.16)	0.24 (0.34)	-0.08 (0.15)
Monthly	-0.34 (0.44)	0 (0.32)	0.21 (0.14)	-0.17 (0.2)	0.04 (0.1)
Every 3 months	1.06 (0.56)*	-0.3 (0.31)	-0.06 (0.14)	-0.49 (0.24)**	0.01 (0.12)
Every 6 months	0.42 (0.44)	0.29 (0.48)	0.34 (0.17)**	-0.02 (0.24)	0.17 (0.14)
Annually	-0.32	1.53	-0.31	-0.04	0.08
Side-effects: Dizziness	0.35 (0.32)	0.04 (0.15)	-0.03 (0.08)	-0.04 (0.14)	0.06 (0.09)
Stomach cramps	-1.23 (0.54)**	-0.3 (0.21)	0.01 (0.09)	-0.07 (0.16)	-0.01 (0.09)
Nausea	0.77 (0.27)***	-0.06 (0.19)	-0.06 (0.09)	-0.26 (0.24)	-0.44 (0.23)*
No side-effects	0.10	0.31	0.09	0.38	0.39
Opt out: Opt out	3.94 (1.35)***	1.02 (1.15)	1.81 (0.19)***	6.39 (1.48)***	0.51 (0.52)
Male condom (opt out)	0.53 (0.04)***	-5.45 (1.15)	1.33 (0.21)***	0.13 (0.27)	0.86 (0.35)**
Class membership probabilities					
Constant	0.23 (0.93)	-1.09 (1.17)		0.94 (1.56)	

Female sex worker	1.98 (0.77)**	1.83 (0.96)*	-
Adolescent	0.99 (0.46)**	1.42 (0.65)**	-
Age	-0.06 (0.03)**	-0.02 (0.04)	-0.04 (0.07)
Experience of IPV in last 12 months	-0.14 (0.17)	-0.19 (0.23)	-
Unhappy if self/partner became pregnant	0.03 (0.14)	0.16 (0.19)	0.06 (0.22)
High HIV knowledge	-0.47 (0.15)***	-0.56 (0.21)***	-0.15 (0.28)
Alcohol use at last sex	0.34 (0.34)	1.01 (0.33)***	0.25 (0.46)
Report external partners in last 3 months	0.03 (0.36)	-0.12 (0.44)	-0.02 (0.21)
Unemployed	0.10 (0.18)	0.03 (0.24)	0.08 (0.21)
Log-likelihood	-4608.94		-1971.39
AIC	9365.90		4012.80

Nb. Standard errors not retrievable in latent class specification for base categories "SILCS diaphragm", "Injectable", "Annually", and "No side-effects". ***, **, * ==> Significance at 1%, 5%, 10% level. Models for each population analysed separately, and indicated as significant if different from zero.

HIV knowledge (as assessed through the tool presented in Supplementary Material 1) is a key driver of demand for HIV protection as Class 1 members (34% of the female sample) show strong preferences for STI and pregnancy protection but do not value HIV protection in a new product. Class membership is additionally predicted by being of younger age, a FSW, or an adolescent, indicating that there is significant variation in preferences among female groups. A HIV preventive MPT would offer substantial benefit to this group of women, as contraceptive or STI preventative products could be bundled with HIV protection, offering additional protection.

In contrast, members of class 2 (19% of the sample) display very strong preferences for HIV protection, valuing it more than twice as highly as other classes. Class 2 members also value pregnancy protection, but do not find STI protection appealing. Class 2 appears to be a high-risk group as, relative to class 3, members are more likely to have used alcohol the last time they had sex, and have lower HIV knowledge. Finally, class 2 members are more likely to be FSW or adolescent girls than class 3 members, and indicate a dislike for coitally-specific products. Class 3 members (48% of the sample) strongly value protection from HIV, pregnancy and STIs, and indicate a dislike for the vaginal ring product. This group is likely to comprise of adult women in the general population.

Among adult males, membership of either class (42%) is not significantly predicted by the characteristics we define, indicating that drivers of preference heterogeneity differ between men and women and that male preferences are not shaped by structural risks in the same manner as female preferences. However, there is still evidence of heterogeneity in preferences among adult men. The most notable variation between the two groups is the non-significance of the pregnancy prevention parameter among class 2 men indicating that, in order to make HIV prevention products attractive to these men, potential HIV and STI prevention properties should be emphasised. Men in class 1

strongly prefer oral PrEP, whilst the strongly significant opt-out parameters in both groups show an inclination to continue current practice suggesting that the expected reporting bias towards switching to new products may not be as strong as hypothesised.

Marginal effects

DCEs estimate the relative strength of preferences, and therefore we cannot simply compare the magnitude of coefficients across groups. However, the ratios of coefficients are comparable across populations and show the variation in trade-offs across groups. The marginal effects of factors relative to the common denominator of HIV protection are provided in supplementary Table 3, computed from the coefficients in Table 3. Adult men are only willing to forgo 3% HIV protection for a contraceptive product, but adult women are willing to forgo 11%. Results suggest that all female groups value the male condom substantially more than men, and that preferences for STI protection is broadly comparable to pregnancy protection across female groups. Men value the absence of side-effects much more than women and FSWs value STI protection almost three times greater than any other group.

Discussion

This study assessed preferences for new HIV prevention products among adult men and women, adolescent girls, and female sex workers. Consistent with prior expectations HIV protection was the most important attribute to respondents, particularly those with high levels of HIV knowledge, however, results suggest that demand would increase for all groups if multipurpose protection was incorporated. There was relatively little variation in preferences for oral PrEP, microbicide gel, the SILCS diaphragm and the vaginal ring when compared to strong preferences for a long-lasting injectable ARV. This could be influenced by the strong awareness and use of injectable contraceptives in South Africa.⁵⁴

This study also provides evidence to explain data from clinical trials of new HIV prevention products. Neither adult women nor adolescent girls found the vaginal ring appealing, whilst an injectable product was favoured by all groups. In the context of trial data suggesting that younger women were not able to adhere to vaginal ring use to the same extent as older women^{8,9}, these results suggest that younger women in particular do not favour a vaginal ring prevention system. Incorporating multipurpose properties to a vaginal ring could mitigate some of the intrinsic dislike of this product, however, these data suggest that a vaginal ring product will not be an attractive offering for younger populations.

Importantly this study suggests that, in order to fully catch the attention of AGYW, products must not be single-purpose but provided to offer multipurpose prevention against HIV, pregnancy, and other STIs. AGYW have been identified as key populations in HIV prevention, and it is critical that new biomedical products are made to be attractive and easy for these women to use.³ Although MPT products are generally at the concept stage of development, bundling PrEP with other sexual and reproductive health

services may make it more attractive than vertical programmes until such time as an MPT is licensed.

Although there are some similarities across groups, the divergence in preferences shown here can provide useful information for programming. Adolescent and adult females are unlikely to be put off by minor side-effects and demonstrate comparable, statistically significant preferences for STI and pregnancy protection. Adult women, however, are much more likely to find the male condom appealing relative to new products, indicating that demand for ARV-based prevention may be less among older, lower-risk women who may prefer on-demand methods. Products rolled out into higher-risk groups (such as AGYW) are more likely to be cost-effective – as long as they can be used consistently and effectively.⁵⁵ Findings from the latent class analysis show notable segments in the market for PrEP, with some women very concerned about HIV and STI protection, and others who are not at all. In addition, female sex workers demonstrate a much stronger preference for STI protection than any other group, perhaps because STI acquisition is more likely to immediately affect earnings than HIV or pregnancy.⁵⁶

Finally, these results suggest that a one size-fits all HIV prevention package will not be an effective or efficient use of resources. This is consistent with recent trajectories of contraceptive and HIV research where it has been recognised that a range of options can optimise uptake and adherence.⁵⁷ Because groups have different preferences and needs, further highlighted by these results, there is a strong case for greater tailoring of prevention services, for at risk young women in particular.

This study has some limitations. Firstly, DCEs are hypothetical tools and may not correlate perfectly with real-world choices. However, recent evidence shows that DCEs conducted in health fields predict real world choices with a relatively high sensitivity, suggesting a reasonable degree of external validity.⁵⁸ Overall, the random sample of the general population survey design and the similarity of sample descriptive statistics with

other representative surveys mean findings may have relevance for other South African settings. Self-reported rates of condom use among males and adolescent girls were higher than other representative surveys and may indicate acceptability biases in reporting, or that condoms were more readily available to this group than others. This study did not include a price attribute, and therefore does not enable the calculation of willingness to pay estimates for different products. However, given the South African context where prevention products will likely be free-of-charge to potential users in the public sector, including a price element would have made the choice task unrealistic. Product profiles in the DCE do not perfectly match with candidate products in development, for example injectable trials are based on administration every eight weeks rather than every four or twelve explored in this DCE, whilst rare but serious side-effects were not included in the choice tasks. In addition, injectable products may be more likely to initiate drug resistance as they have been shown to remain in the body at a low level⁵⁹, and this is not included here. Finally, there is a lively literature discussing the reliability of RDS to generate generalisable samples suggesting that, at worst, RDS is a superior form of convenience sampling for hard-to-reach populations and, at best, produces bias-free and generalisable samples.^{32, 60}

Further research is needed to estimate the impact and cost-effectiveness of potential single- and multi-purpose HIV prevention products. If models do not incorporate the variation in product preferences that we observe here and instead assume an average uptake across groups, they may give misleading results. Because models are used to generate impact predictions for investment cases in low- and middle-income countries (e.g. in South Africa⁶¹), inaccurate predictions could result in reduced efficiency in the allocation of resources, and large opportunity costs in terms of benefits forgone. This paper shows that particular attention should be paid to the perspectives of different groups of end-users.

Conclusion

This study involved a discrete choice experiment among four groups in Ekurhuleni Municipality in South Africa. In general, respondents indicated a strong desire for products that are highly effective in preventing HIV infection. However, there was strong demand across all groups for multipurpose prevention products to protect against other STIs and pregnancy. Further analysis shows substantive heterogeneity across and within groups, suggesting that a variety of prevention methodologies are required to meet the demands of different groups. These results strengthen the call for effective and attractive multipurpose prevention technologies to be deployed as part of a comprehensive combination prevention strategy.

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Supplementary file 1: HIV Knowledge tool

Here are some statements about protection against HIV. For each statement please tell me whether you think it is true or not.

1. Coughing and sneezing openly DOES NOT spread HIV.
2. A person can get HIV by sharing a glass of water with someone who has HIV.
3. A woman can get HIV if she has anal sex with a man
4. Showering, or washing one's genitals/private parts, after sex keeps a person from getting HIV.
5. It is possible for a HIV positive mother to give birth to a HIV negative child
6. A person can get HIV by sitting in a hot tub or a swimming pool with a person who has HIV.
7. Being circumcised reduces a man's chance of getting HIV from a woman
8. If a HIV positive person takes HIV treatment regularly, they are less likely to transmit HIV to a sexual partner

Supplementary Table S1: Exploring heterogeneity

Segment type (concepts)	Variables	Anticipated effect on HIV/pregnancy
Sociodemographic	Sub-population membership (FSW, Adolescent)*	?/?
	Age	?/?
Structural drivers of HIV risk	Exposure to IPV in previous 12 months*	+/+
	Unemployed	?/?
	Alcohol use at last sex	+/+
Lifestyle and risk	Would be unhappy if became pregnant*	?/+
	External partner in previous 3 months	+/+
	High HIV knowledge	+/?
	Circumcised ¹	+/?

* => Applicable to female groups only

¹ => Applicable to male groups only

Supplementary Table S2: MNL main effects results

	Adult Males Coeff. (SE)	Adult Females Coeff. (SE)	Adolescent Girls Coeff. (SE)	FSW Coeff. (SE)
Products: Oral PrEP	-0.11 (0.074)	-0.31 (0.11)***	0.09 (0.19)	-0.41 (0.097)***
Microbicide Gel		-0.17 (0.14)	-0.12 (0.23)	-0.38 (0.119)***
Vaginal Ring		-0.16 (0.11)	-0.28 (0.18)**	0.03 (0.099)
SILCS Diaphragm		-0.16 (0.21)	-0.19 (0.33)	-0.38 (0.178)**
Injectable	0.11 (0.074)	0.8 (0.28)***	0.5 (0.16)	1.14 (0.214)***
Protection: HIV protection	3.53 (0.289)***	2.33 (0.53)***	2.59 (0.88)***	2.19 (0.425)***
Pregnancy prevention	0.11 (0.034)***	0.16 (0.05)***	0.48 (0.09)***	0.14 (0.044)***
STI protection	0.48 (0.046)***	0.22 (0.06)***	0.44 (0.1)***	0.36 (0.048)***
Frequency of use: Daily	-0.05 (0.112)	0.17 (0.16)	0.05 (0.28)	0.21 (0.136)
Coitally		0.14 (0.23)	0.47 (0.37)**	0.18 (0.193)
Weekly	0.08 (0.116)	0.15 (0.23)	-0.27 (0.25)*	-0.18 (0.122)
Monthly	0.03 (0.078)	0.4 (0.13)***	0.17 (0.22)	0.27 (0.105)***
Every 3 months	-0.19 (0.096)**	0.06 (0.12)	0.03 (0.24)	-0.11 (0.113)
Every 6 months	0.11 (0.106)	0.01 (0.13)	-0.12 (0.26)	-0.07 (0.117)
Annually	0.02 (0.029)	-0.93 (0.15)**	-0.34 (0.26)	-0.3 (0.285)
Side-effects: Dizziness	0.01 (0.063)	-0.13 (0.07)*	-0.12 (0.13)	-0.18 (0.061)***
Stomach cramps	-0.03 (0.063)	0.07 (0.08)	0.11 (0.16)	-0.01 (0.077)
Nausea	-0.27 (0.113)***	0.02 (0.08)	0.01 (0.13)	-0.17 (0.067)**
No side-effects	0.29 (0.078)***	0.05 (0.05)	0.01 (0.07)	0.02 (0.023)
Opt out: Opt out	3.06 (0.244)***	2.05 (0.4)***	2.95 (0.41)***	1.68 (0.362)***
Male condom	0.01 (0.054)	0.6 (0.09)***	0.16 (0.09)*	1.2 (0.174)***
Log-likelihood	-2317.7	-2107.85	-1998.34	-3240.41
AIC	4663.5	4251.7	4032.7	6516.8

***, **, * ==> Significance at 1%, 5%, 10% level. Coefficients for omitted categories retrieved through calculating $-1 \times \sum(\text{coeffs.})$. Models for each population analysed separately, and indicated as significant if different from zero. 100% HIV protection modelled.

Supplementary Table S3: MMNL marginal effects relative to HIV

	Adult Males	Adult Females	Adolescent Girls	FSW
Pregnancy protection	3%	11%	7%	15%
STI protection	14%	13%	10%	38%
No side-effects	10%	4%	2%	4%
Male condom	3%	88%	26%	103%

Supplementary file 2

The following section presents the results of a brief further analysis carried out on the DCE survey data, including interaction specifications to explore observable heterogeneity among participants. We interact a number of respondent characteristics with DCE attributes to explore associations between observable characteristics and preferences for HIV and pregnancy protection.

MNL Interaction Specification

We explore observable heterogeneity among the four populations by running separate MNL models with interaction terms between HIV, STI, and pregnancy protection alongside individual characteristics. Results are presented in supplementary Table S4, and show a great deal of variation in how sociodemographic characteristics affect preferences across groups. For example, exposure to intimate partner violence increases the importance of HIV protection to adult women, but not adolescents or FSWs. Alcohol use at last sex is associated with an increased importance of HIV protection among men and sex workers, but a decreased importance among adult and adolescent women. Having high HIV knowledge increases utility gained from HIV protection among adolescent girls, but there is no significant effect in other populations. Adult men who are circumcised value HIV protection from a new product less than uncircumcised men.

Preferences for contraceptive properties are higher among adolescents not in work (including those still in education). Exposure to IPV has a mixed effect between FSWs and adolescents, increasing preferences for contraceptive properties among FSWs but diminishing their importance among adolescents. Adolescents and FSWs who reported that they would be unhappy if they fell pregnant today valued contraceptive properties more than those who would be happy or indifferent, however there was not association among adult women.

The design interactions, between HIV, STI and pregnancy protection, indicate a substantial preference for multipurpose pregnancy and STI products across all female groups indicating intrinsic benefits from multipurpose prevention. There is evidence that preferences for multipurpose products vary across groups with evidence that demand may reduce for products offering HIV and STI protection among adult males and females.

Supplementary Table S4: MNL model with interaction effects

	Adult Males	Adult Females	Adolescent Girls	FSW
Products: Oral PrEP	-0.21 (0.111)*	-0.19 (0.12)	0.24 (0.13)*	-0.43 (0.109)***
Microbicide Gel		-0.12 (0.16)	0.15 (0.16)	-0.24 (0.133)*
Vaginal Ring		-0.33 (0.11)***	-0.39 (0.13)***	-0.09 (0.111)
Injectable		0.05	0.11	-0.31
SILCS Diaphragm		0.59 (0.36)	-0.1 (0.35)	1.07 (0.284)***
Protection: HIV protection (100%)	4.61 (0.533)***	1.75 (0.71)**	0.56 (2.53)	3.75 (0.649)***
Pregnancy prevention	-0.06 (0.298)	-0.03 (0.45)	1.49 (1.41)	1.52 (0.393)***
STI protection	1.66 (0.255)***	1.03 (0.29)***	0.51 (0.3)*	0.73 (0.235)***
Frequency of use: Daily	0.12 (0.136)	-0.22 (0.21)	-0.57 (0.2)***	-0.42 (0.171)**
Coitally		-0.2 (0.25)	0 (0.25)	-0.29 (0.225)
Weekly	0.23 (0.141)*	0.14 (0.15)	-0.29 (0.17)*	-0.54 (0.134)***
Monthly	0.12 (0.09)	0.3 (0.17)*	0.12 (0.19)	0.8 (0.147)***
Three-monthly	-0.35 (0.141)**	0.28 (0.15)*	0.03 (0.17)	-0.35 (0.134)***
Six-monthly	-0.11 (0.129)	0.19 (0.17)	0.18 (0.17)	0.25 (0.125)**
Annually	-0.01	-0.49	0.54	0.55
Side effects: Dizziness	-0.03 (0.066)	-0.1 (0.09)	-0.05 (0.09)	-0.31 (0.081)***
Stomach cramps	-0.11 (0.066)*	0.05 (0.09)	0.05 (0.1)	-0.01 (0.085)
Nausea	-0.07 (0.127)	0 (0.09)	-0.02 (0.1)	0.28 (0.088)***
No side effects	0.21	0.05	0.03	0.04
Opt out: Opt out	3.14 (0.264)***	1.9 (0.41)***	3.13 (0.41)***	2.35 (0.385)***
Male condom (opt out)	0.06 (0.056)	0.54 (0.1)***	0.5 (0.11)***	1.26 (0.175)***
Design interactions				
HIV*STI	-0.03 (0.006)***	-0.02 (0.01)***	-0.002 (0.01)	-0.005 (0.006)
Pregnancy*STI	0.11 (0.125)	0.3 (0.13)**	0.74 (0.13)***	0.78 (0.098)***
Pregnancy*HIV	0.005 (0.003)	-0.0002 (0.01)	0.002 (0.01)	-0.02 (0.004)***
Sociodemographic interactions				
Age*HIV	0.02 (0.08)**	0.04 (0.002)***	0.06 (0.14)	0.02 (0.011)
IPV exposure in last year*HIV		0.43 (0.12)***	-0.06 (0.13)	0.03 (0.062)
Unemployed*HIV	-0.04 (0.072)	0.13 (0.08)	-0.27 (0.16)*	0.04 (0.06)
Alcohol use at last sex*HIV	0.28 (0.093)***	-0.01 (0.14)***	-1.77 (0.7)**	0.84 (0.085)***
External partners*HIV	-0.15 (0.082)*	-0.09 (0.08)	0.7 (0.26)***	-0.43 (0.088)***
High HIV Knowledge*HIV	-0.08 (0.065)	0.06 (0.08)	0.2 (0.07)***	-0.04 (0.052)
Age*pregnancy	-0.01 (0.004)***	-0.001 (0.004)	0.09 (0.07)	-0.01 (0.006)
IPV exposure in last year*pregnancy		0.01 (0.04)	-0.24 (0.06)***	0.13 (0.035)***
Unemployed*pregnancy	-0.01 (0.036)	0.05 (0.03)	0.24 (0.09)***	0.03 (0.034)
Alcohol use at last sex*pregnancy	-0.03 (0.042)	-0.08 (0.07)	0.16 (0.49)	-0.04 (0.038)
External partners*pregnancy	-0.07 (0.041)*	-0.04 (0.04)	-0.14 (0.11)	-0.01 (0.048)
Unhappy if fell pregnant now*pregnancy		-0.11 (0.07)	0.37 (0.08)***	0.11 (0.045)**
Circumcised*HIV	-0.001 (0.001)**			
Log Likelihood	-2291.17	-2070.14	-1940.97	-3099.83
AIC	4636.3	4206.3	3947.9	6265.7

Conclusions from paper R1

The results presented in this paper offer important insights into preferences for MPTs among different South African population groups. In particular, they suggest that MPTs will be attractive options for many women, but preferences vary across – and within – different groups. Yet it is necessary to go beyond these results to fully inform policy, as the potential benefit of these products cannot be extrapolated from these data. For example, the alternatives shown were restricted to those available to male or female participants, which meant that choices reflect preferences under perfect agency to choose. Yet, due to a range of cultural and socio-economic reasons, the choices of women in many contexts are restricted by the preferences of their male partners, which we did not capture.

The next paper uses these DCE results to predict product uptake among female groups to assess the potential impact and cost-effectiveness of a range of MPT introduction scenarios.

Chapter 7: Paper R2 – The cost-effectiveness of multipurpose HIV and pregnancy prevention technologies in South Africa

Overview of paper R2

Although paper R1 demonstrates that MPTs are likely to be attractive products in South Africa, in isolation these results are not sufficient to support continued investment in MPT development. This paper estimates the cost-effectiveness of combinations of candidate multipurpose prevention technologies (MPTs), which could be co-formulated or co-provided for dual HIV and pregnancy protection, in South Africa among general population women and female sex workers (FSWs).

Uptake predictions from the DCE are used to parameterise a simple, static product impact model for five potential MPTs: intravaginal ring, injectable ARV, microbicide gel, and SILCS diaphragm used in concert with gel. A cost model was created to estimate the health system costs of product delivery, including product and staff costs for MPT delivery and averted costs from averted HIV infections and unintended pregnancies. Product benefit was estimated in disability-adjusted life years (DALYs) averted. Benefits from contraception were incorporated through adjusting the uptake of these products based on the DCE and through estimating the costs averted from avoiding unwanted pregnancies.

The paper is presented as submitted to *The Journal of the international AIDS Society* in May 2017. A range of supplementary materials, including the description of the cost model, are included immediately after the paper. These are not presented in the manuscript itself due to the journal's word limit.

This paper fulfils research objective 2 to estimate the impact and cost-effectiveness of new HIV prevention products among South African men, women, adolescent girls and FSWs.



RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Matthew Quaife
Principal Supervisor	Fern Terris-Prestholt
Thesis Title	Using stated preferences to estimate the impact of new HIV prevention products in South Africa

If the Research Paper has previously been published please complete Section B. If not please move to Section C

SECTION B – Paper already published

Where was the work published?	
When was the work published?	
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	
Have you retained the copyright for the work?*	Was the work subject to academic peer review?

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Journal of the International AIDS Society
Please list the paper's authors in the intended authorship order:	Matthew Quaife, FFP, BE, MF, MHB, MM, GMR, SDM, PV
Stage of publication	Submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	helped out analysis, wrote first draft, incorporated co-author comments
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Student Signature: _____

Date: 17/7/17

Supervisor Signature: _____

Date: 17/7/17

The cost-effectiveness of multi-purpose HIV and pregnancy prevention technologies in South Africa

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Keywords: HIV prevention, multi-purpose prevention, discrete choice experiments, pre-exposure prophylaxis, key populations, South Africa

Ethical Statement: The study was reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee (M140614) and the Research Ethics Committee at the London School of Hygiene and Tropical Medicine (8541-2). All participation in the DCE and supporting qualitative studies was voluntary and subject to completion of a written informed consent process. Adolescent participants were asked

for written assent, in addition to written consent provided by a parent or guardian per South African law.

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Author Contributions: Conceived, designed and tested the DCE: MQ FTP RE MC SDM PV. Analysed the data and developed the cost-effectiveness model: MQ FTP PV. Wrote and revised the manuscript: MQ FTP RE MC SDM MM MKB GMR PV.

Abstract

Introduction: multi-purpose

A number of antiretroviral HIV prevention products are efficacious in preventing HIV infection. However, the sexual and reproductive health needs of many women extend beyond HIV prevention and research is ongoing to develop multi-purpose prevention technologies (MPTs) that offer dual HIV and pregnancy protection. We do not know if these products will be an efficient use of constrained health resources. In this paper we estimate the cost-effectiveness of combinations of candidate multi-purpose prevention technologies (MPTs), in South Africa among general population women and female sex workers (FSWs).

Methods: We combined a cost model with a static model of product impact based on incidence data in South Africa to estimate the cost-effectiveness of five candidate co-formulated or co-provided MPTs: oral PrEP, intravaginal ring, injectable ARV, microbicide gel, and SILCS diaphragm used in concert with gel. We accounted for the preferences of end-users by predicting uptake using a discrete choice experiment (DCE).

Product availability and protection were systematically varied in five potential rollout scenarios. The impact model estimated the number of infections averted through decreased incidence due to product use over one year. The comparator for each scenario was current levels of male condom use, while a health system perspective was used to estimate discounted lifetime treatment costs averted per HIV infection. Product benefit was estimated in disability-adjusted life years (DALYs) averted. Benefits from contraception were incorporated through adjusting the uptake of these products based on the DCE and through estimating the costs averted from avoiding unwanted pregnancies. We explore the additional impact of STI protection through increased uptake in a sensitivity analysis.

Results: At central incidence rates, all single- and multi-purpose scenarios modelled were cost-effective among FSWs and women aged 16-24, at a governmental willingness-to-pay threshold of \$1,175/DALY averted (range: \$214 to \$810/DALY averted among non-dominant scenarios), however none were cost-effective among women aged 25-49 (minimum \$1,706/DALY averted). The cost-effectiveness of products improved with additional protection from pregnancy. Estimates were sensitive to variation in incidence assumptions, but robust to other parameters.

Conclusions: To our knowledge, this is the first study to estimate the cost-effectiveness of a range of potential MPTs; suggesting that MPTs will be cost-effectives amongst higher incidence FSWs or young women but not lower incidence older women. More work is needed to make attractive MPTs available to potential users who could use them effectively.

Introduction

Over the past six years, clinical trials have shown that antiretroviral (ARV)-based pre-exposure prophylaxis (PrEP) can be efficacious in preventing the transmission of human immunodeficiency virus (HIV)¹⁻⁵. However, protection has been variable during clinical trials and different PrEP modalities have conferred substantially less protection to younger women than older women^{4 6}. Both oral and topical PrEP products have been more effective in male populations than females^{7 8}, partly explained by adherence, and partly by pharmacokinetic data indicating higher drug colorectal drug concentrations than in the female lower genital tract^{6 9}.

It is likely that more than one effective prevention option will be needed to achieve population coverage amongst women¹⁰. One option to increase impact whilst making products more desirable to potential users is to develop multi-purpose prevention technologies (MPTs), which simultaneously provide protection from two or more of HIV, other STIs and unintended pregnancy¹¹⁻¹⁴. Current MPTs in development include: 1) long-acting drug delivery systems such as intravaginal rings, designed to protect from HIV infection and pregnancy (currently in phase-1 trial, ClinicalTrials.gov Identifier: NCT02235662); 2) pericoital drug delivery systems such as vaginal gels, tablets and films (not currently being trialled); and 3) co-provision of a combination of products, such as a contraceptive diaphragm with microbicide gel (currently feasible but not widely implemented)^{11 15}. In the medium term, the co-provision of contraceptive and HIV preventative products could be an intermediate step to the development of a MPT. As HIV prevention products come to market, provision alongside contraceptives – particularly when products are of the same modality – could facilitate uptake and adherence, and gauge demand for potential MPTs in the future.

Despite large variations in effectiveness and cost assumptions, previous studies have broadly found single-purpose PrEP to be cost-effective when delivered to populations at high risk of HIV infection¹⁶⁻²⁰. Although the financial and regulatory burden of MPT

development is likely to be high, their benefits may also be large, not least because of synergistic impacts across health outcomes. Firstly, products offering more than one indication may be more attractive to some potential users than single-purpose products, particularly the combination of contraceptive and HIV prevention properties^{21 22}. Secondly, MPT use could *crowd-in* protection from lesser valued attributes. For example, where users value contraceptive properties strongly, additional HIV protection would be a positive externality from the use of a dual-protective product. In addition, we can use lessons learnt in contraceptive provision for different female populations to optimise MPT or co-provision modalities²³. Thirdly, the contraceptive properties of MPTs may reduce the stigma associated with accessing HIV prevention tools, shown to be a substantive barrier to use^{24 25}.

Unlike other PrEP impact models which use expert opinion to inform uptake assumptions, we take a data-driven approach by using a discrete choice experiment (DCE) to predict product uptake among different groups²⁶. DCEs are economic tools which ask people to choose between hypothetical alternatives, and have been shown reliable when predicting real-world choices^{27 28}. Although relying on hypothetical choices, a DCE is useful because preferences can be elicited for products which do not exist yet, thus we can estimate demand for co-formulated or co-provided products containing contraceptive properties. DCEs are objective, end-user focused tools which may be less biased than predictions based on expert opinion^{22 29}.

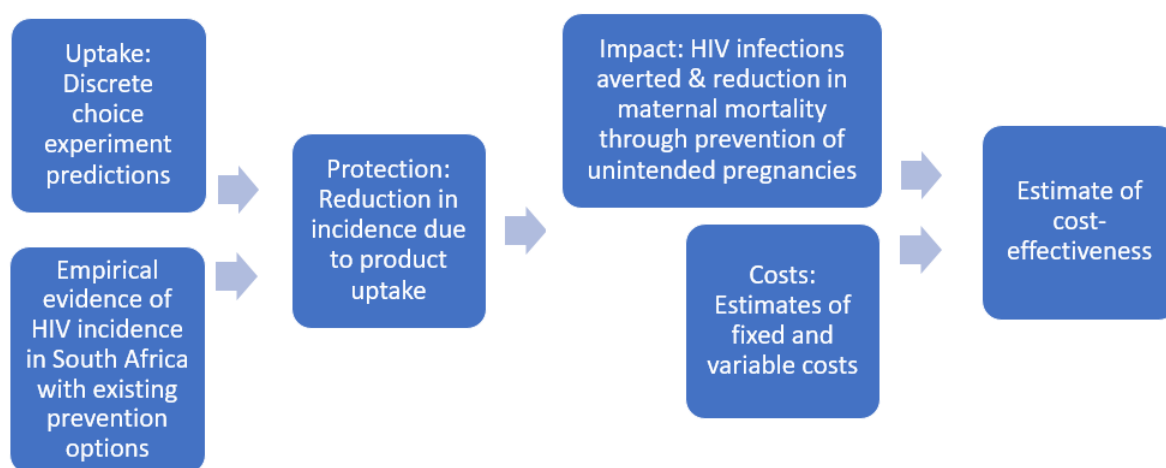
This paper presents a cost-effectiveness analysis which estimates the incremental benefits and health system costs of single and multi-purpose prevention products, compared to current practice of condom use and male circumcision prevalence. Cost-effectiveness is modelled across three female groups due to differences in epidemiology and HIV risk in each: younger women (aged 16-24), older women (aged 25-49), and female sex workers (FSWs).

Methods

Analytic overview

This analysis builds on previous work using a DCE to elicit preferences for new HIV prevention products in South Africa²². Figure 1 displays our approach to estimate the cost-effectiveness of the five single and multi-purpose prevention products considered: oral PrEP, intravaginal rings, injectable ARVs, microbicide gels, and SILCS diaphragms used in concert with gel. A full list of parameters used in the model is presented in supplementary file S1. In this paper, we focus on contraceptive MPTs (considering STI prevention in a sensitivity analysis) because no STI-specific MPT is in development whilst there are limited data on the efficacy of MPT products to prevent STIs. We model cost and benefits associated with one-year's products use, and therefore do not consider variations over time such as increasing economies of scale or diminishing adherence patterns.

Figure 6: Modelling schematic



Estimating uptake

DCE data were gathered in Ekurhuleni Municipality, South Africa between September and December 2015 from 484 self-reported HIV negative women: 362 from the general population and 122 FSWs. We use DCE data to simulate uptake for different scenarios of

MPT characteristics (Table 1) in each population. In the model, users choose one product (or continue current practice) from a set, where availability is defined by different policy scenarios set out in the next section. The DCE protocol and results are described in detail elsewhere ^{26 30}, whilst further information is given in supplementary file S2.

Table 1: Product characteristics

Product characteristics	HIV efficacy (% _x), [PSA bounds]	Contraceptive protection	Freq. of use	Product cost assumptions (\$USD)	Source
Single-purpose					
Oral PrEP	61 [40-75]	N	Daily	75 [70-130] (/person-year)	31 32 19
Microbicide gel	55 [31-71]	N	Coitally	3.69 [3-4.5] (/tube)**	Manufacturer (Kessel ³³)
SILCS diaphragm	55 [31-71]	N	Coitally	5.19 [4-6] (/diaphragm)	Manufacturer (Kessel ³³)
Vaginal ring	55 [31-71]	N	Monthly	6 [5-7] (/ring)	Distributor (IPM ³⁴)
Injectable ARV agent	75 [55-90]	N	Three monthly	6 [5-7] (/injection)	Assumption from vaginal ring
<i>No condom</i>	<i>0</i>	<i>N</i>	<i>Coital</i>	N/A (comparator)	
Multi-purpose				Marginal direct cost of MPT	
Male condom	95 [66-94]	Y	Coital	N/A (comparator)	
MPT oral PrEP	61 [40-75]	Y	Daily	8.72 [6.17-11.5] (/person-year)	35
MPT microbicide gel	55 [31-71]	Y	Coitally	9.14 [6.4-12] (/person-year)	35
SILCS diaphragm & microbicide gel	55 [31-71]*	Y	Coitally	-	
MPT vaginal ring	55 [31-71]	Y	Monthly	9.14 [6.4-12] (/person-year)	Assumed equal to highest cost product (injectable) ³⁵
Injectable MPT agent	75 [55-90]	Y	Three monthly	9.14 [6.4-12] (/person-year)	35

*Due to co-use, the efficacy of the SILCS diaphragm was assumed the same as the microbicide gel

**Assumptions on product use and other associated costs of provision listed fully in supplementary file 3

Rollout scenarios

We modelled product uptake for five rollout scenarios that differed in product characteristics and availability. Table 2 shows the scenarios modelled, for all of which we use current practice as the base case for comparison. Scenario 1 is the most likely to occur first, as single-purpose oral PrEP is already available to FSW groups in South Africa³⁶. Cautiously positive results from intravaginal ring trials⁵ indicate that a single-purpose ring with HIV prevention may be introduced next, whilst a multi-purpose ring could be available in the medium term; we refer to this MPT ring plus PrEP scenario as scenario 3¹¹. Finally, we model the introduction of a varied suite of single then multi-purpose products in scenarios 4 and 5 respectively. Although poor efficacy in clinical trials has seen the HIV prevention field move away from microbicide gels⁸, we include them here to inform the development of other topical ARV-based preventative methods, including vaginal tablets or films³⁷.

Table 2: Product scenarios modelled

	Product(s)	HIV protection	Pregnancy protection
Reference-scenario	Current male condom usage. No ARV-based single- or multi-purpose prevention		
Scenario 1	Oral PrEP	X	
Scenario 2	Oral PrEP	X	
	Vaginal ring	X	
Scenario 3	Oral PrEP	X	
	MPT vaginal ring	X	X
Scenario 4	Oral PrEP	X	
	Intravaginal ring	X	
	Injectable ARV agent	X	
	Microbicide gel	X	
	SILCS diaphragm & microbicide gel	X	X
Scenario 5	MPT oral PrEP	X	X
	MPT vaginal ring	X	X
	Injectable MPT agent	X	X
	MPT Microbicide gel	X	X
	SILCS diaphragm & microbicide gel	X	X

Estimating HIV protection

To be conservative, and to focus on differences between populations and the relative preferences for different products, we do not model temporal reductions in the overall level of HIV transmission due to long- term product use. Instead, we model the yearly impact of introducing each product scenario among three female population groups in South Africa, and compare the total and incremental costs and benefits of each introduction scenario.

We use formula (1) to estimate the impact of each product scenario on the average level of protection conferred to an individual^{22 38}. This measure gives the average decrease in HIV transmission probability across a population for an average sex act, combining the protection provided from several products with different efficacies being used at different levels. For a single product x , we assume the average protection against HIV, p_x , from using product x is a function of its efficacy, E_x , and uptake (or use) U_x ,

$$p_x = E_x U_x \quad (1)$$

We begin by denoting P_x as the existing protection provided by male condoms with efficacy E_0 and consistency of use U_0 , before any new products are introduced. Our DCE then gives projections of the degree to which condom users and non-condom users (defined by use at last sex act) uptake each new product in each scenario s , and for condom users the probability that the woman still uses the condom (ε) in addition to the new products. For scenario s involving a number m of new products (denoted by subscript $i=1\dots m$), each with efficacy E_i^s and differing uptake $U_{i,c}^s$ amongst condom users ($c=1$) and non-condom users ($c=0$), respectively, the average protection provided provided to an individual in the population due to condoms and the introduction of m new products (not just amongst users of the product) is estimated as P_m^s :

$$P_m^s = U_0 \left[E_0 - \sum_{i=1..m} U_{i,1}^s (1 - \varepsilon) E_0 + (1 - \varepsilon) \sum_{i=1..m} E_i^s U_{i,1}^s \right. \\ \left. + \varepsilon \sum_{i=1..m} (1 - E_0) E_i^s U_{i,1}^s \right] + (1 - U_0) \sum_{i=1..m} E_i^s U_{i,0}^s \quad (2)$$

The uptake of each product amongst condom and non-condom users depends not only on the efficacy of the product for preventing HIV but also on whether they provide pregnancy protection. The prevention protection provided by different products is assumed to be additive. Users are assumed to use only one new ARV-based prevention product, except the diaphragm and gel which are necessarily used together for MPT protection. When condoms are used with a new product, the new product was assumed to proportionately decrease the remaining risk still existing after the 85% protection provided by the condom³⁹. The uptake of each new product $U_{i,c}^s$ can be defined as uptake multiplied by adherence, and we vary the latter in a one-way sensitivity analysis and both in probabilistic sensitivity analysis.

For oral PrEP, we assumed an HIV efficacy of 61% (40-75% used in probabilistic sensitivity analysis) as found in a recent meta-analysis of the efficacy of oral PrEP amongst highly adherent women (>75% adherence)⁴⁰. We then assume that the vaginal ring is introduced with a HIV efficacy of 55% (31-71% used in probabilistic sensitivity analysis), as found amongst older women in a recent trial⁴¹. Although some clinical trials of microbicide gels have shown a lack of efficacy, they have been shown to be efficacious in others and work continues to develop a gel which could also offer multi-purpose protection¹¹. We assume that a microbicide gel would not be introduced if it was less effective than the next-least effective product, in this case the vaginal ring, and we use the same uncertainty bounds and allow each to vary in probabilistic simulations. A higher efficacy for HIV protection of 75% (55-90% used in probabilistic sensitivity analysis) was assumed for injectable ARVs because there should be fewer issues of adherence.

Estimating DALYs averted through preventing HIV infection

Our simple impact model estimates the number of infections averted through one year's use of different product scenarios, where incremental protection, P_m^s , is used to decrease HIV incidence. We estimate the total discounted lifetime treatment costs averted from these infections. We use World Bank estimates of the size of the general population in South Africa in 2017 among two female groups aged 16-24 and 25-49⁴² and apply HIV prevalence estimates from the South African HSRC National HIV Prevalence, Incidence and Behaviour Survey 2012⁴³ to estimate the HIV negative population in each group. For FSWs, we used national estimates of FSW population size and HIV prevalence in South Africa^{44 45}. Standard DALY weights are used for HIV/AIDS with and without ART taken from the 2010 Global Burden of Disease study⁴⁶, full details of the DALY calculations are listed in supplementary files S1 and S3.

We obtained group level incidence estimates from national surveys, as well as from recent HIV treatment and prevention trials in South Africa^{40 43 47 48} presented in Table 3. For each group, we model scenarios of low, central and high estimates of incidence. The level of protection provided by each scenario, P_m^s , is used to model a decrease in incidence:

$$Incidence_{new} = Incidence_{current} * (1 - P_m^s) \quad (3)$$

Table 3: Estimates of HIV incidence per 100 person years

	Low Incidence	Central Incidence	High Incidence	Reference
Females 16-24	1.62	2.54	5.00	41 48 49
Female 25-49	1.20	1.62	3.50	41 48 49
FSW*	3.50	5.00	8.00	8

* No FSW incidence data found, instead high level female incidence figures were used

Estimating unintended pregnancies averted

We take the median projected unmet need for contraception among females in the general population as defined by the United Nations Population Division ⁵⁰, and assume that FSWs who report using no method of contraception have unmet need. Informed by DCE estimates, in the initial comparison case we assume that 20% of women with unmet need will use products with contraceptive properties, and explore how variation in this parameter affects results in a sensitivity analysis. Following the family planning literature, DALYs are averted solely from the reduction in estimated maternal mortality from pregnancies averted through MPT use^{51 52}.

Estimating costs

We estimate costs related to the delivery of a combination prevention package across all South African public clinics from a health system perspective. Included intervention costs are listed in Table 4, and details of their estimation given in supplementary file S3. Products have varying frequencies of collection and use which we model using realistic clinical use scenarios, informed by the South African national guidelines for PrEP rollout

among high risk groups³⁶. Where MPT products do not yet exist, we used existing contraceptive product costs to account for costs of additional active compounds³⁵. Lifetime averted costs were estimated by multiplying the number of HIV infections and unwanted pregnancies averted by the discounted lifetime cost of ART treatment (using estimates of life expectancy on ART ⁵³), and delivery, or abortion costs respectively.

Table 4: Included intervention costs

Fixed costs	National start-up costs	Training of providers Mass media
Variable costs (based on predictions of use)	Facility distribution costs	Staff time Product Screening tests Health system mark-up and overheads
	Averted health costs	Antiretroviral treatment Miscarriages and births from unplanned pregnancies

Sensitivity analyses

We present results for each group and each scenario at high, medium, and low incidence estimates. In addition, we perform a series of one-way deterministic sensitivity analyses to explore how changes in qualitatively important characteristics affect estimates. Finally, a probabilistic sensitivity analysis (PSA) explored the sensitivity of our model to a range of parameter uncertainties, using a Monte Carlo simulation with 1000 draws. Point estimate and distributional assumptions for the variables included in the PSA are listed in supplementary file 1, and results presented in supplementary file 8.

Assessment of cost-effectiveness

We assessed the cost-effectiveness of different scenarios by computing the incremental cost-effectiveness ratio (ICER) for each intervention: the net costs of an intervention divided by the number of DALYs averted, and compare this to a willingness-to-pay (WTP) threshold. The South African government does not have a generally accepted

WTP threshold; in the absence of this we use the threshold estimates of Woods et al⁵⁴ to represent the opportunity cost of health forgone from other potential interventions. We took a conservative stance and applied the lowest estimate, the lower-bound USD threshold of \$1,175/DALY averted (range: \$1,175-\$4,714), which was lower than the purchasing-power adjusted range (\$2,221-\$8,909) and alternative thresholds such as 1x and 3x GDP/capita^{54 55}.

Results

Deterministic model analysis

Results suggest that co-provision or co-formulation of contraceptive and HIV prevention products will be cost-effective among younger women and FSWs, but not among older women. Younger women show distinct preferences for multi-purpose over single-purpose products as shown in Figure 2 which aggregates uptake among condom and non-condom users. Notably, we predict that just 8% of women aged 16-24 would use at least one of the full range of single-purpose HIV prevention products, however uptake increases by 27 percentage points if products were co-formulated as MPTs. The predicted uptake of single-purpose products is much greater among older women (26%) and FSWs (30%), but additional uptake from including pregnancy protection is relatively low at 7 and 6 percentage points respectively. Where all products are introduced, the decrease in HIV incidence attributable to additional uptake due to multi-purpose protection was higher among younger women (reduction of 19%) than among other groups (8% for older women and FSWs).

Of the 12.9 million women aged 15-49 in 2017, 10.1 million were estimated to be HIV negative⁴³. Assuming central HIV incidence estimates, 201,552 new HIV infections are predicted to occur without intervention. Figure 3 illustrates DALYs averted for each product scenario among each population group. We focus here on cost-effectiveness, but present full impact results in supplementary file S6. Net intervention costs are presented in supplementary figure S7, where rollout among the 1.7-times larger population of women aged 25-49 leads to a four-fold increase in net intervention costs than among those aged 16-24.

Figure 4 shows ICERs for each product scenario and population group. For all groups, oral PrEP plus a MPT intravaginal ring (Scenario 3) is the most cost-effective scenario modelled, with an ICER of \$563/DALY averted among younger women and dominating

the comparator among FSWs. All scenarios modelled among women aged 16-24 and among FSWs are cost-effective when compared to the WTP threshold of \$1,175, whilst the no rollout status quo scenario is cost-effective among women aged 25-49. Among all populations, scenarios where multi-purpose products are introduced are more cost-effective than any combination of single-purpose products.

These results show the cost-effectiveness of interventions relative to current levels of condom use, yet the increasing availability of oral PrEP in South Africa mean that a more meaningful comparator may be that of oral PrEP provision. Table 5 displays ICER estimates for introducing single- and multi-purpose products, with the comparator of oral PrEP and the range of single-purpose products that may be available. Again, results indicate that at under all incidence assumptions, introducing additional ARV-based prevention products will be cost-effective among women aged 16-24 and FSWs. Results differ among women aged 25-49, where introducing additional MPT products is estimated to be cost-effective (in most cases cost-saving), but adding a single-purpose ring to provision of single-purpose PrEP is not cost-effective except under assumptions of high incidence.

Table 5: ICER values of comparative scenarios

	Women 16-24			Women 25-49			FSW		
Incidence assumption	Low	Central	High	Low	Central	High	Low	Central	High
<i>Single-purpose</i>									
Adding vaginal ring to PrEP (Scenario 2 compared to Scenario 1)	\$1,691	\$801	\$30	\$4,763	\$3,282	\$1,008	\$792	\$-66	\$-398
<i>Multi-purpose</i>									
Adding MPT ring to PrEP (Scenario 3 compared to Scenario 1)	\$727	\$243	\$-225	\$-401	\$-482	\$-669	\$-532	\$-709	\$-791
Adding MPT range to single-purpose range (Scenario 5 compared to Scenario 4)	\$1,214	\$543	\$-79	\$88	\$-114	\$-503	\$-1,810	\$-1,502	\$-1,334

*Negative ICER values in this table indicate cost-saving interventions with a positive impact

Figure 2: Product uptake by group

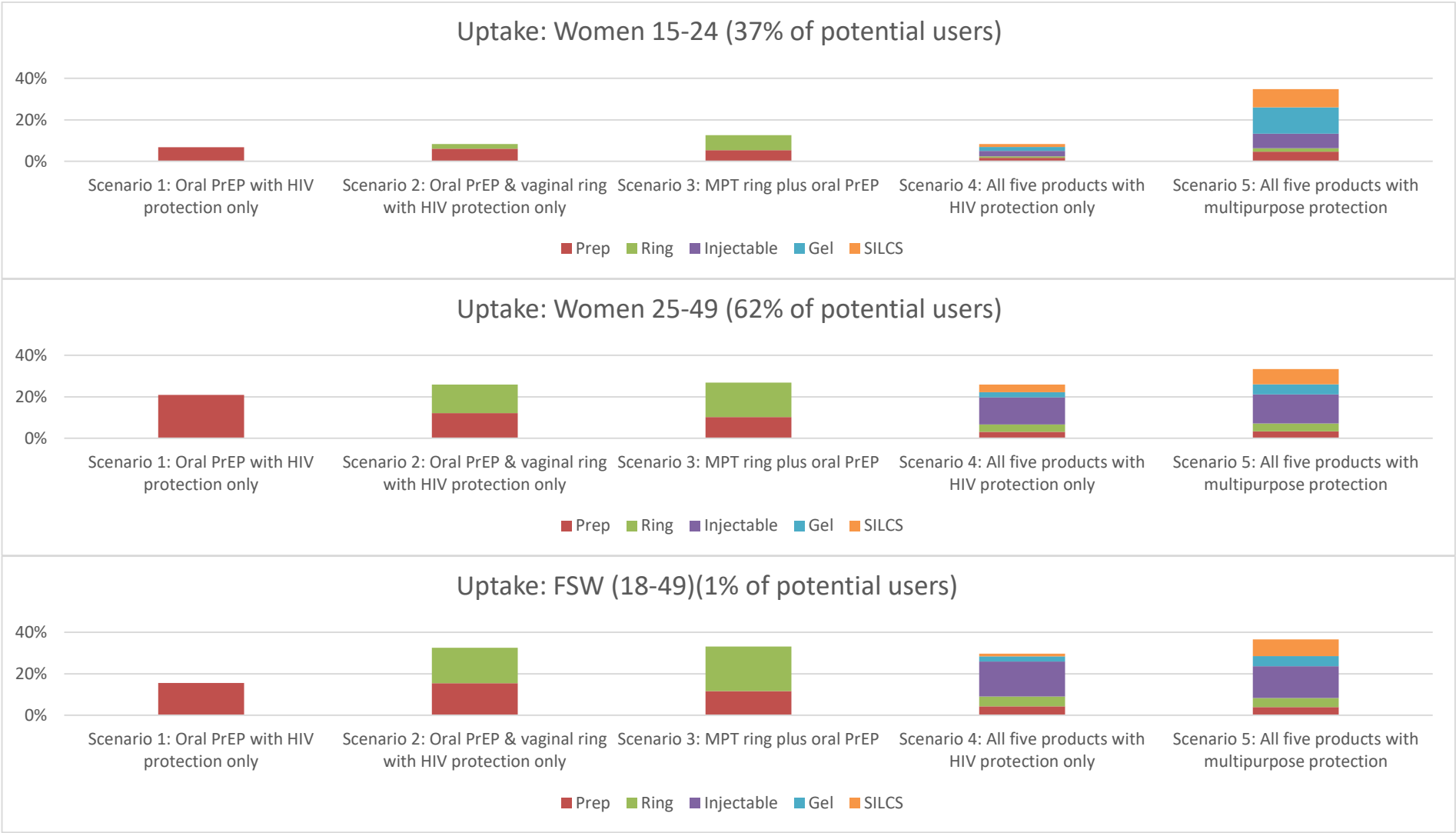
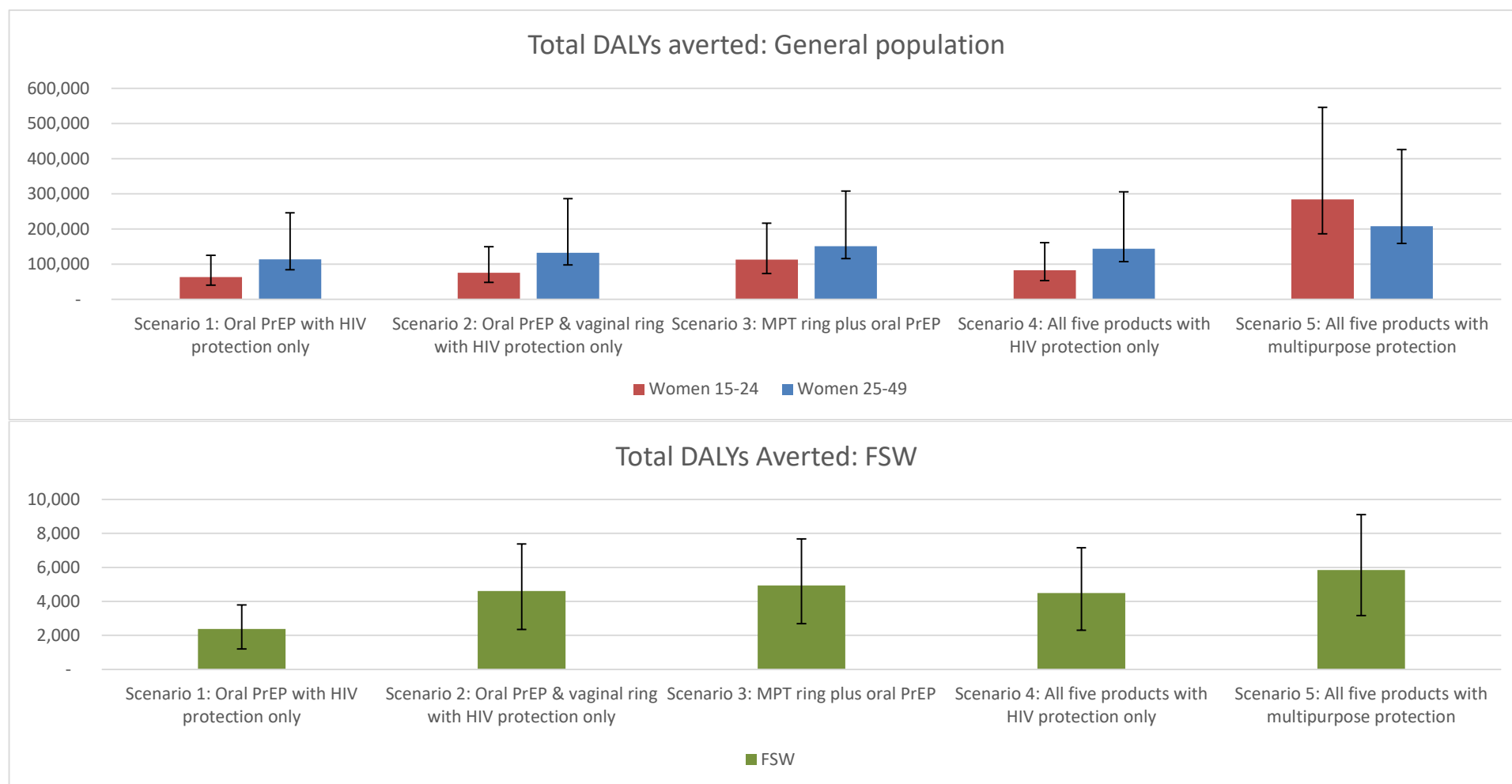
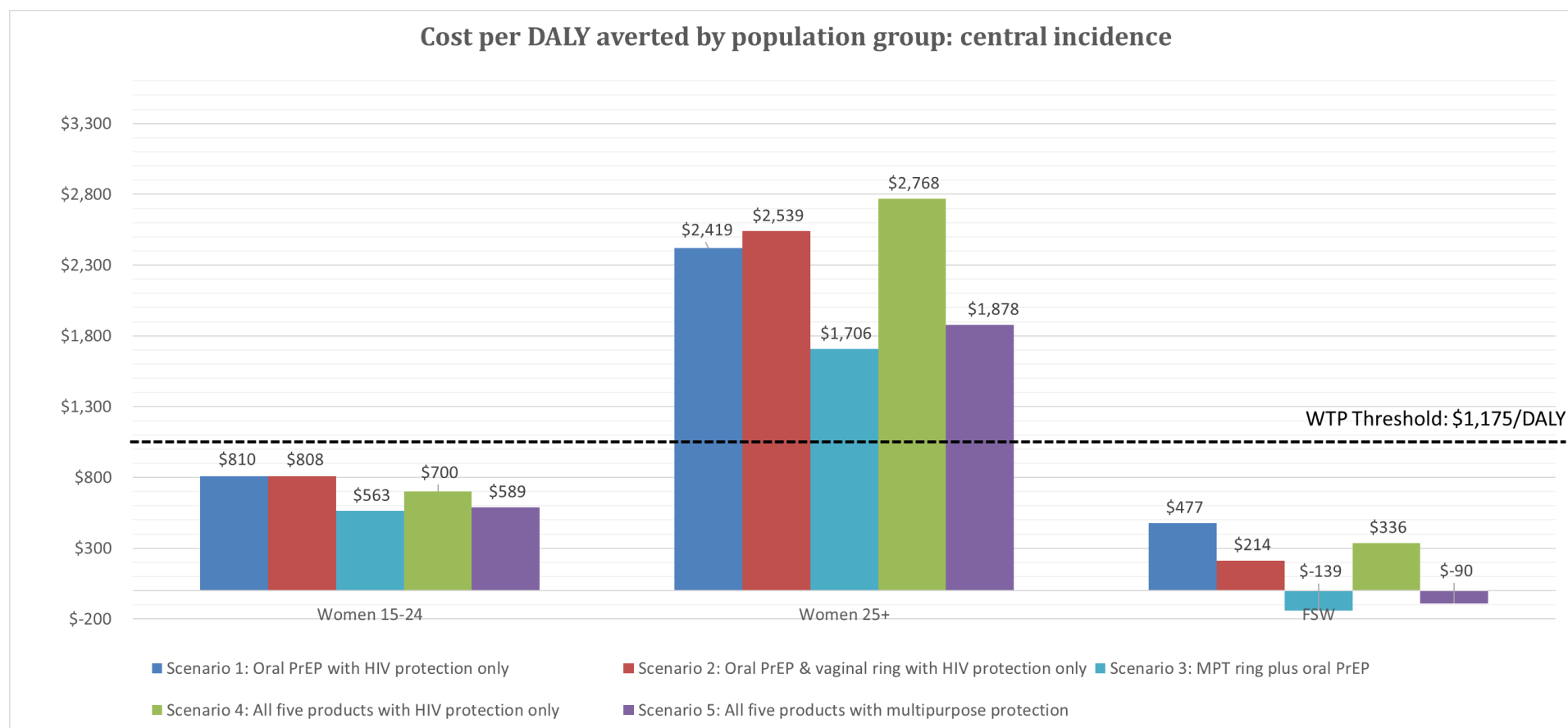


Figure 3: DALYs averted by population, scenario, and incidence assumption



Coloured bars represent DALYS averted at central incidence estimates, with upper and lower incidence assumptions indicated for each scenario. Populations presented separately due to scale differences in small FSW population.

Figure 4: Average cost per DALY averted by scenario and incidence assumption



Nb. Negative ICERs among FSWs are cost-saving and DALY increasing interventions with a positive impact.

Figure 5: One-way sensitivity analysis on incidence assumptions

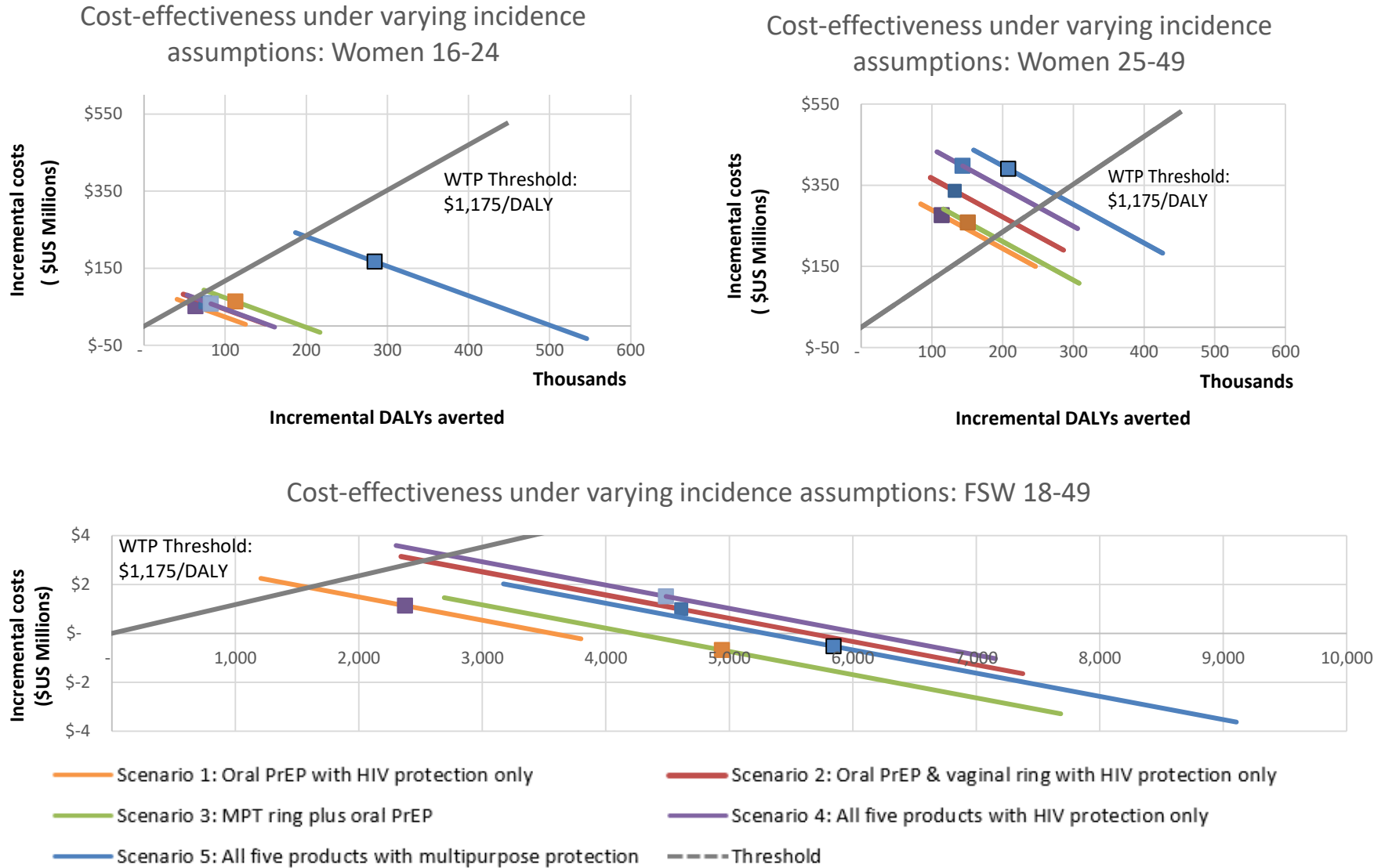
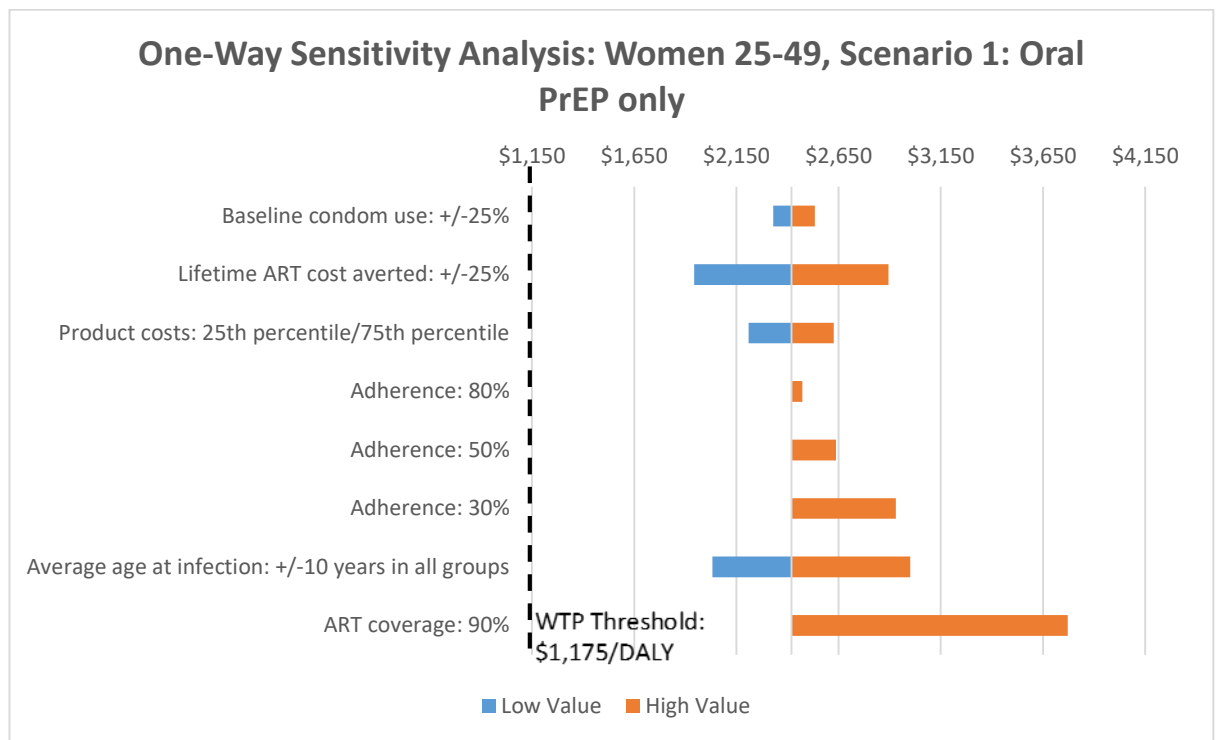
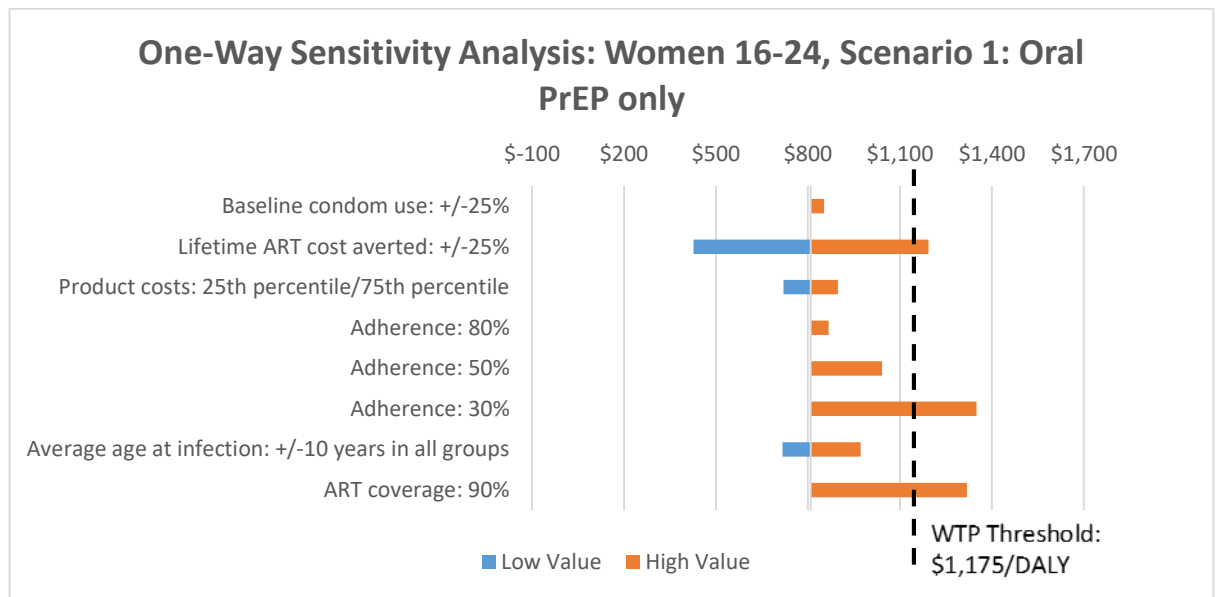
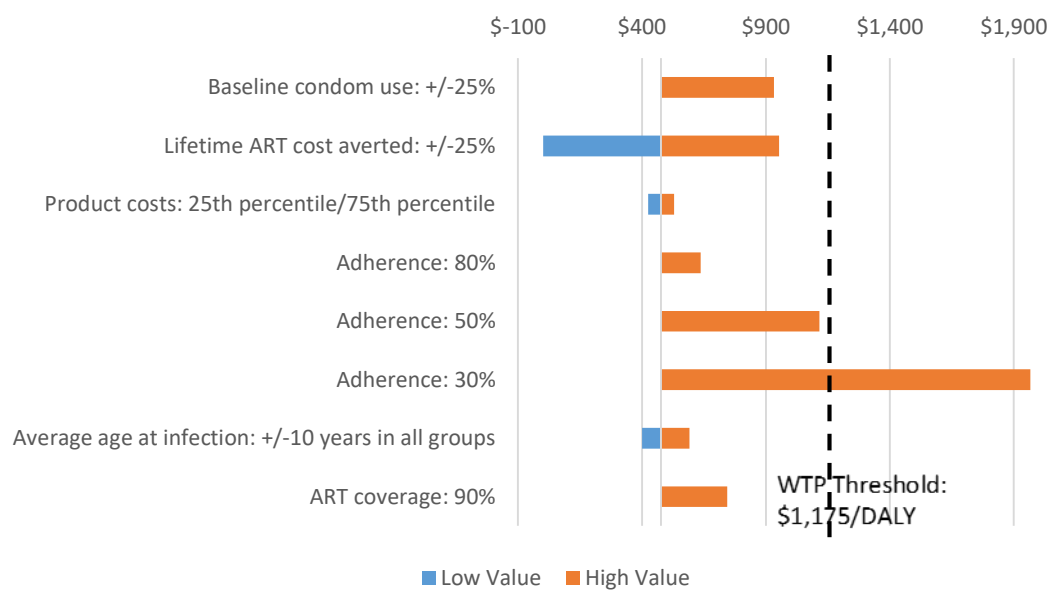


Figure 6: One-way sensitivity analyses of scenario 1



One-Way Sensitivity Analysis: FSW 18-49, Scenario 1: Oral PrEP only



Sensitivity analyses

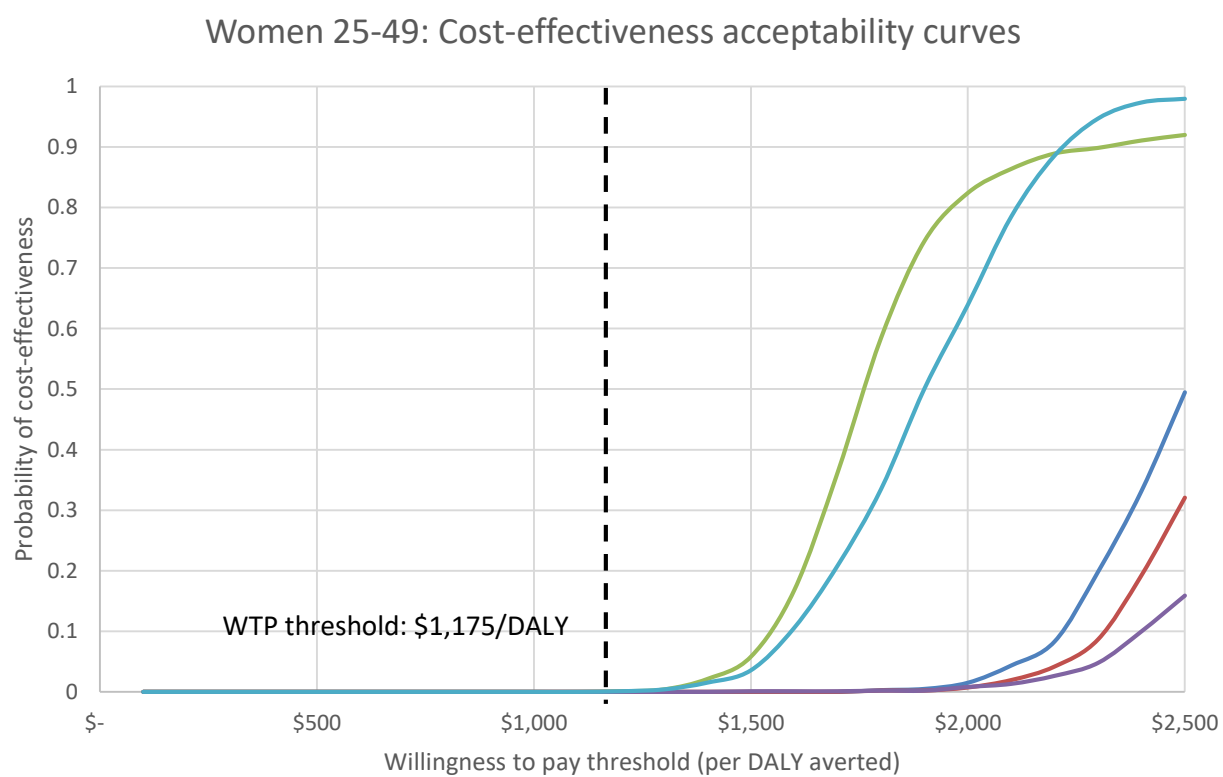
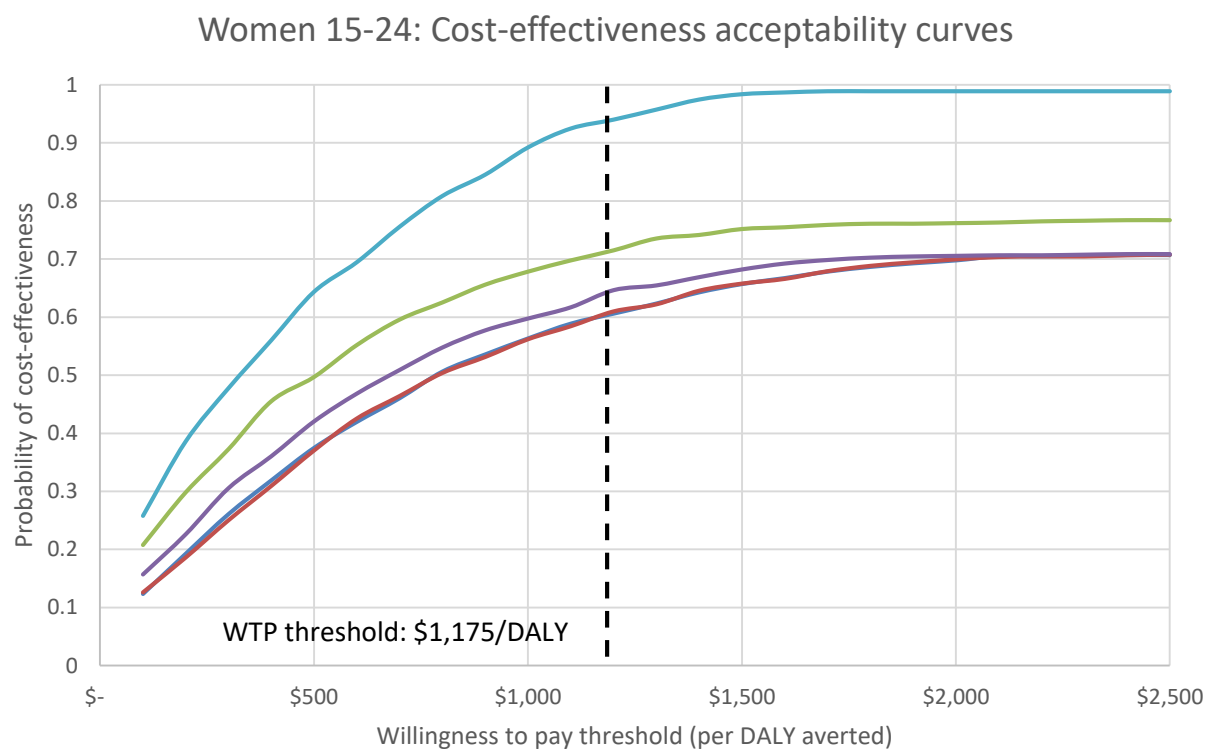
Figure 5 shows one-way sensitivity analyses for incidence assumptions. Our base case model assumptions are represented by squares, whilst lines to the upper-left and lower-right demonstrate ICER estimates at lower and upper incidence assumptions respectively. Points to the south-east of the dashed WTP line are interpreted as cost-effective. In all but two scenarios modelled (both among FSWs), using an upper or lower incidence assumption means that the estimated ICER crosses the willingness-to-pay threshold. The incidence level at which the most cost-effective scenario became cost-ineffective was 1.3, 1.6, and 1.1 infections per 100 person-years for women aged 16-24, 25-49, and FSWs respectively.

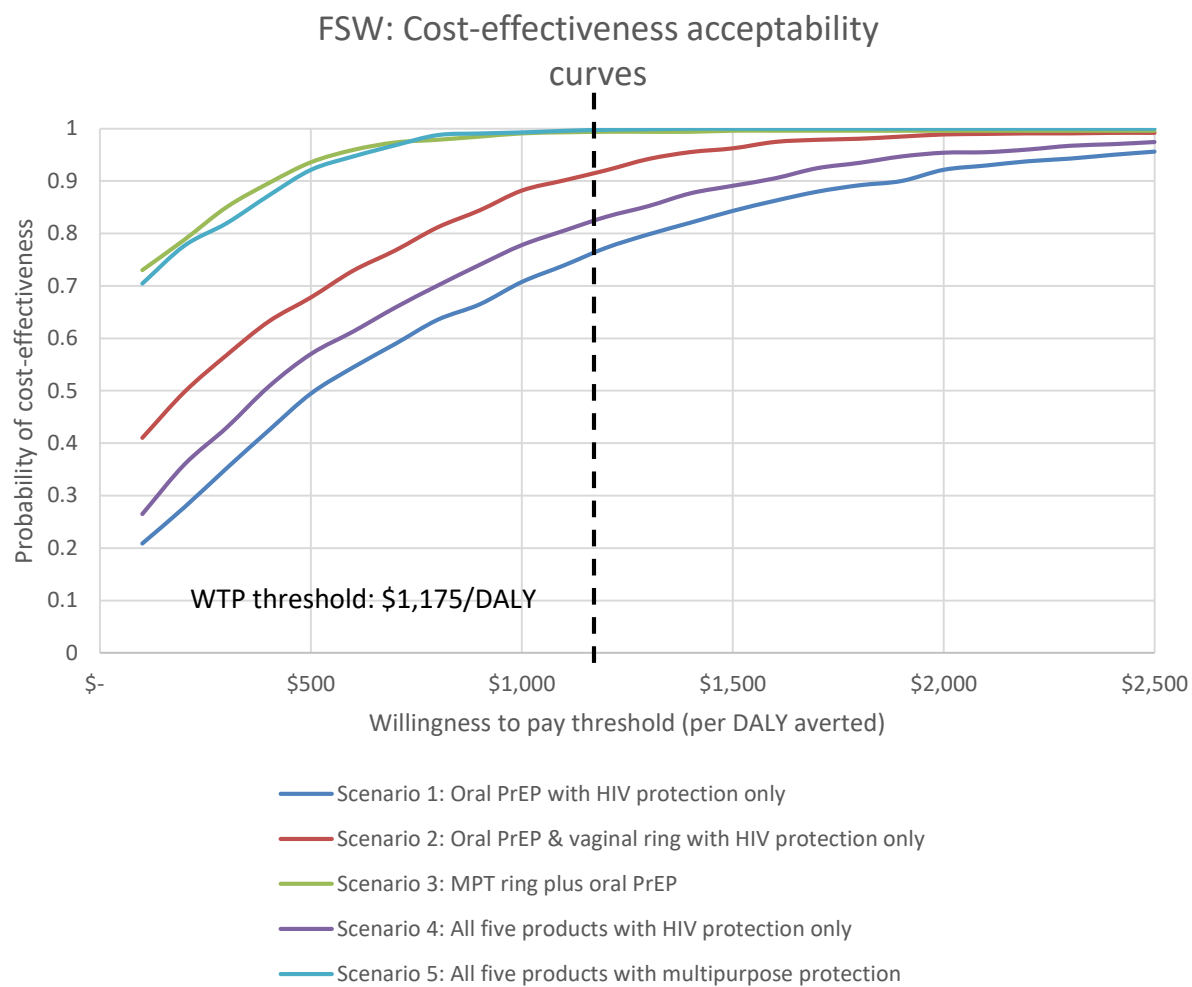
Further one-way sensitivity analyses explored the effect of parameter uncertainty on model outputs. Tornado plots for scenario 1 are presented in Figure 6 which became cost-ineffective among women aged 16-24 and FSWs when adherence was assumed to be 30%, or if ART coverage was increased to meet the 90% WHO target⁵⁶. Including STI preventative attributes in addition to HIV and pregnancy does not markedly change cost-effectiveness estimates. Tornado plots for the most cost-effective scenario (oral PrEP plus MPT ring) are included in supplementary file S6, and demonstrate cost-effectiveness in females aged 16-24 and FSWs for all parameter variations.

MPT cost-effectiveness was broadly robust to reductions in the assumed efficacy of products. Additional one-way sensitivity analyses (not shown in Figure 6) were carried out on assumptions of product efficacy. Reducing the effectiveness of all products to 50% meant that all three scenarios of solely single-purpose products would not be cost-effective among women aged 16-49 (Scenario 1 had the highest ICER of \$1,281), though all MPT scenarios and scenarios among FSWs would remain cost-effective. MPT scenarios among younger women were estimated not to be cost-effective at an efficacy of 45%.

Figure 7 presents cost-effectiveness acceptability curves for each scenario among each population, whilst simulation plots on the cost-effectiveness plane are included in supplementary file S7. For all groups, both scenarios including MPTs were most likely to be cost-effective. For older women, younger women, and FSWs respectively, the model predicts a 0.1%, 71%, and 99% probability that the most cost-effective scenario, scenario 3, will be cost-effective. The PSA also confirms the primacy of interventions among FSWs and women aged 16-24, as even the least cost-effective scenario for each group was 60% likely to be cost-effective at the \$1,175 threshold.

Figure 7: Cost-effectiveness acceptability curves





Discussion

This study is the first to estimate the cost-effectiveness of a range of candidate MPT products, and suggests that co-formulated or co-provided MPTs could be an impactful and efficient use of resources. Based on the stated preferences in the DCE, incorporating contraceptive characteristics into HIV prevention products would result in a meaningful increase in product use, reinforcing evidence of unmet demand for MPTs among many groups^{11 12}. Results indicate that multi-purpose prevention products are likely to be cost-effective among younger women (aged 16-24) and FSWs compared to current condom provision, with scenario 3, oral PrEP plus a MPT ring, and scenario 5, the full range of MPT products, estimated to be the most cost-effective. However, despite being cost-effective, our uptake projections suggest that products are unlikely to achieve dramatic decreases in HIV incidence. Even if all MPT products were introduced, incidence among older women and FSWs is projected to reduce by just 8% (19% among younger women), far under the estimated 48% reduction from achieving UNAIDS' 90-90-90 target⁵⁷. Although MPTs offer a cost-effective option for tackling the HIV epidemic, a range of programmes will be required to reduce incidence substantively.

The co-formulation or co-provision of products is likely to increase programme cost-effectiveness for two reasons. First, the multi-purpose nature of the products makes them more attractive to potential users, increasing uptake and therefore economies of scale from product use. Second, the costs associated with unwanted pregnancies averted reduce the net costs of the intervention overall, and increase benefits accrued from averted maternal mortality. Incorporating STI prevention does not markedly change cost-effectiveness estimates.

These estimates of cost-effectiveness are broadly comparable to published studies, though there is considerable heterogeneity in these²⁰. Although we base our counterfactual scenario on empirical data from trials and nationally representative population based studies, our simple incidence model predicts a higher number of

annual infections than more complex models, such as Thembisa and EPP/Spectrum models^{58 59}. The reason for this is uncertain, although it is worth noting that the both models underestimate the 2012 HIV incidence in South Africa compared to empirical estimates by around 0.4 infections/100 person years among women aged 16-29⁶⁰. Additionally, when incidence is varied in our sensitivity analysis, our results are consistent with other models. We note that the relatively low effectiveness figures observed in topical PrEP trials (e.g.^{5 61}) may reduce the likelihood of governments investing in them, but incorporating additional benefits such as contraception into partially effective products may increase their chances of introduction.

This study has several limitations. First, we used a simple static transmission model to estimate the short-term benefits of introducing different products. This model does not consider prevention benefits accruing into the future, including the dynamic effect of reductions in incidence on prevalence. However, this simplicity is also a strength because it gives transparent estimations of the individual benefits of using these products, resulting in estimates of impact and cost-effectiveness similar to what would be produced from a trial. Unfortunately, although dynamic transmission models can be more realistic in capturing the longer-term benefits of an intervention, their reliance on numerous assumptions, particularly around the future dynamics of infection, makes their projections uncertain. Indeed, a recent analysis of 12 models for South Africa showed that none were able to correctly predict the future dynamics of infection between 2006 and 2011⁶². Importantly, our use of a static model results in conservative impact projections, as a dynamic model would predict increased numbers of secondary infections averted with product use. However, when new preventive methods are used by a small proportion of the population, as predicted here, total population protection has been shown similar to a static model of efficacy multiplied by use⁶³, suggesting our model projections may be fairly accurate.

Second, the model does not incorporate differential adherence between products, although the one-way sensitivity analysis shows that adherence could be less than 50% and products still be cost-effective. Third, results are sensitive to incidence assumptions, and 8 of the 10 cost-effective scenarios become cost-ineffective if low HIV incidence assumptions are used. However, a PSA shows that MPT scenarios among FSWs and women aged 16-25 are 99% and 71% likely to be cost-effective at the conservative \$1,175 threshold respectively. Fourth, we do not consider reductions in paediatric HIV incidence due to unintended pregnancies averted, making estimates conservative. Fifth, we consider one-year estimates of cost and benefit from each scenario. In reality, this may overestimate costs due to the potential for economies of scale in delivery over time. Estimates of benefit could also be overestimated, if uptake is graduated over time leading to the level assumed here, or if adherence was assumed to vary over time, reducing as a function of length of use for example. Sixth, we estimate the costs of multi-purpose products to be additive of that to single-purpose products, which may underestimate the true cost of products, particularly if coformulated, in a real-world value-based pricing framework. This means that our cost estimates for MPTs may be too low, making MPTs seem more cost-effective than they may be in reality, however since the estimated costs of oral PrEP are substantively higher than those observed in real-world demonstration projects (e.g. ⁶⁴), the overall impact may be mitigated. Finally, although single-purpose contraceptives are available for all delivery mechanisms modelled (oral, injectable and topical products), there is variation in which mechanisms are being developed for co-formulation to provide multi-purpose prevention. The introduction of a range of five MPTs is unlikely to occur in reality.

This paper is also the first to use a discrete choice experiment to predict product uptake within a cost-effectiveness analysis in HIV, which allows us to explicitly consider heterogeneity in end-user preferences between different groups. While DCE survey data were randomly sampled and reweighted to match the age structure of the female South

African population, these data are unlikely to be generalisable to the entire country or other countries. Furthermore, the FSW data were collected through respondent driven sampling (RDS) and, although reweighted, the highly variable nature of sex work in South Africa makes reliable statements about generalisation difficult⁴⁵.

Conclusion

This study estimates the cost-effectiveness of five candidate MPTs, and finds that co-formulation or co-provision of contraceptive and HIV prevention products would be an efficient and effective use of resources among younger female groups and FSWs at current levels of HIV incidence. Younger women in particular find MPTs more attractive than single-purpose technologies, suggesting that incorporating contraceptive properties in HIV prevention products – or vice-versa – could lead to substantive HIV and family planning benefits in this group. These results strengthen calls for more research and development in the co-formulation or co-provision of products to reduce unmet need in sexual and reproductive health services.

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Supplementary Material for:

The cost-effectiveness of combined HIV and pregnancy protection: An economic evaluation of multipurpose prevention products in South Africa

Supplementary file S1: List of model parameters: cost-effectiveness model

Parameter	Point estimate	Lower Credible Interval/95%CI	Upper Credible Interval/95%CI	PSA Distribution (SE where included)	Source(s)
Cost inputs					
Product variable costs (per person year)					
Oral Prep	\$289	\$269	\$309	Uniform*	See supplementary material S3
Vaginal Ring	\$258	\$243	\$273	Uniform*	See supplementary material S3
Injectable	\$212	\$192	\$230	Uniform*	See supplementary material S3
Microbicide Gel	\$438	\$349	\$516	Uniform*	See supplementary material S3
SILCS Diaphragm and Microbicide Gel	\$217	\$199	\$235	Uniform*	See supplementary material S3
Product fixed costs					
Staff training across all facilities	\$34,696,831				Conservative assumptions using staff salary costs. 3 days, 100 staff each training day from four facilities (25 per facility), 5 nurse facilitators
Mass media (annual)	\$5,000,000				(1)
Outreach cost	\$403,920				Assumption based on FSW sample size, one clinic with 12 outreach staff per 1,500 FSWs
Population sizes					
Females 15-24	4,810,897				(2)
Female 25-49	8,156,317				(2)
FSW	153,000	132,000	182,000	Uniform	(3)
HIV Prevalence					
Females 15-24	11%	10%	13%	Normal (0.009)	(4)

Female 25-49	29%	27%	32%	Normal (0.014)	(4)
FSW	74%	59%	83%	Normal (0.049)	(4)
HIV Incidence**					
Females 15-24	2.54	1.62	5.00	Uniform	(5-7)
Female 25-49	1.62	1.62	3.50	Uniform	(5-7)
FSW	5.00	2.54	8.00	Uniform	(8)
Contraception parameters					
Percentage of women married/in union (relationship) from data	86%	82%	90%	Beta (0.022)	Primary data
Percentage of women in relationship with unmet contraceptive need	72%	66%	78%	Beta (0.030)	Primary data
Percentage of FSWs with unmet contraceptive need	16%	11%	21%	Beta (0.026)	Primary data
Probability of getting pregnant using product (year) (perfect use)	14%	18%	14%		SILCS, winner NEJM (9, 10)
Likelihood of becoming pregnant with no product (/year)	40%				(11)
ART costs (year)	4,586.99				(12)
Parameters for DALY calculations					
Discount rate	0.03	3%	7%		
Age weighting modulation factor	1				(13)
Constant	0.1658				(13)
parameter from the age weighting function	0.04				(13)
DALY Weight: pre-ART	0.051				(14)
DALY Weight: symptomatic, not linked to care	0.221				(14)
DALY Weight: on ART	0.053				(14)
DALY Weight: AIDS	0.547				(14)

DALY Weight: Infertility	0.006				(14)
ART Access rate	0.72				(15)
Product Efficacy					
Oral Prep	61%	40%	75%	Uniform	(16)
Vaginal Ring	56%	31%	71%	Uniform	(6)
Injectable	75%	55%	90%	Uniform	Assumption based on lower adherence requirement, large uncertainty bound modelled
Microbicide Gel	85%	66%	94%	Uniform	Assumption that a microbicide gel would not be introduced if it was less effective than the next-least effective product (vaginal ring)
SILCS Diaphragm and Microbicide Gel	56%	31%	71%	Uniform	Assumption that a microbicide gel would not be introduced if it was less effective than the next-least effective product (vaginal ring)

* Separate PSA was carried out on cost-model inputs as described in supplementary file S3. A uniform distribution used here so as to not prescribe a functional form on the results of this PSA, and to allow greater uncertainty around these estimates into the final model

** Uniform distribution used on incidence assumptions to avoid prescribing a specific functional form to these data, largely obtained from trials

Supplementary file S2: Information on DCE and the impact model

DCE data were gathered in October to December 2015 in Ekurhuleni Metropolitan Municipality through a randomised household survey among 158 adult females and 204 adolescent girls (aged 16-17), who self-reported as HIV negative, and data were reweighted by two age strata to the general population structure of South African women(18). A respondent driven sampling process collected data for 122 FSWs from the same geographical area, which was reweighted using RDSAT software(19, 20).

Figure S2:1: Example DCE task presented to participants:

Here are the products and this is what they do. Please select the product you would most prefer.

1	A	B	C
Product	Vaginal ring	Injection	Injection
HIV protection	95% risk reduction 19 of 20 people remain HIV negative	55% risk reduction 11 of 20 people remain HIV negative	95% risk reduction 19 of 20 people remain HIV negative
Pregnancy prevention	Does not prevent pregnancy	Prevents pregnancy	Does not prevent pregnancy
Frequency of use	Use once per month	Use two times per year	Use four times per year
Protection against other infections	STI Protection Does not prevent STIs	STI Protection Does not prevent STIs	STI Protection Prevents STIs
Side effects	Stomach cramps/pain	No Side Effects	Dizziness

OR

Nothing	Condom
	Condom
0% risk reduction 0 of 20 people remain HIV negative	95% risk reduction 19 of 20 people remain HIV negative
Does not prevent pregnancy	Prevents pregnancy
Never	Every sex
STI Protection Does not prevent STIs	STI Protection Prevents STIs
No Side Effects	No Side Effects

DCE data are used to predict uptake through predicted probability analysis, as described in earlier work.(21) Briefly, coefficients from DCE nested logit utility functions are summed according to expected characteristics of potential prevention products as shown in table 1 such that:

$$P_{n,i} = \frac{e^{V_{n,i}}}{\sum_{j=1}^J e^{V_{n,i}}}$$

DCE analysis is based on the assumption that people make rational choices to maximise utility.(22) By analysing what respondents choose in ten hypothetical choice sets presented to them, we are able to compute the probability of a respondent making a

specific product choice depending on the characteristics of that product (based on real-world attributes of products), and defining what other products are available and their characteristics.(21) This method of simulating from choice data has been termed predicted probability analysis (PPA), and has been applied in fields of health, environmental and transport economics.(23, 24) Although the DCE presented MPT options as co-formulations, these results could also inform the co-provision of contraceptive and HIV preventative products.

We estimate uptake among condom users and non-condom users for each scenario and among each population, and use data from the primary survey to assume that condom use in partnership with new products is 60%. In the probabilistic sensitivity analysis, variation in DCE coefficients (and therefore uptake) is simulated through drawing from a normal distribution using the mean and standard error reported by the discrete choice model. All DCE coefficients are varied in this manner.

Impact model

Formula 1 firstly takes the original protection provided by condoms ($U_0 E_0$), removes the loss in protection due to new product users stopping using condoms ($U_0 \sum_{i=1..m} U_{i,1}^S (1 - \varepsilon) E_0$), then adds the new product protection amongst those individuals that stop using condoms ($U_0 (1 - \varepsilon) \sum_{i=1..m} E_i^S U_{i,1}^S$), the new protection amongst new product users that carry on using condoms ($U_0 \varepsilon \sum_{i=1..m} (1 - E_0) E_i^S U_{i,1}^S$), and the added protection of individuals that did not use condoms before but now use the new products ($((1 - U_0) \sum_{i=1..m} E_i^S U_{i,0}^S)$).

Supplementary file S3: The cost model

Cost model methods

This cost model estimates the costs associated with the roll-out of five new antiretroviral(ARV)-based HIV prevention products: oral pre-exposure prophylaxis (PrEP), a microbicide gel, a SILCS diaphragm used in concert with microbicide gel, an intravaginal ring (IVR), and an injectable ARV. The main cost model takes a health system (provider) perspective. It considers the direct medical costs of provision for each method, associated health system costs, and costs averted from HIV infection alongside unwanted or mistimed pregnancies.

As per South African guidelines, we assume that when first prescribed a prevention product, users will be tested for HIV infection immediately and after one month, then returning for a test every third month. We assume that all users receive the services detailed in the guidelines.

We carried out a probabilistic sensitivity analysis which explored the role of parameter uncertainty in the model. Inputs were obtained from published literature or computed from a primary survey carried out in Gauteng Province in late 2015 (survey protocol in appendix IX) and from the 2003 DHS dataset.(11, 25) Where data were unavailable through these sources, we contacted international experts and product-development sources for remaining parameters.

The setting and distribution scenarios

The model represented all South African public health clinics, a large network of 3,182 facilities, as the South African PrEP guidelines indicate that provision will be fully integrated within primary healthcare clinics to mitigate stigmatisation when trying to obtain PrEP.(26) We model that the introduction of the new products is via public facilities, supported by a mass media campaign run annually: for six months prior to

rollout (at double intensity – and thus cost than that which would follow in later years. The model allows for differential demand on staff time by product, however do not include substantial variation across products in the base case in table 2. Different products have different frequencies of collection and use which we model using realistic clinical use scenarios informed by the South African national guidelines for PrEP rollout among high risk groups which requires persons using PrEP to obtain an HIV, and associated other medical, tests every three months.(26) As per these guidelines, we assume that when first prescribed a prevention product, users will be tested for HIV infection immediately and after one month, then returning for a test every third month. Finally, as per these guidelines, users will receive the tests detailed in table 3 before initiation, and during maintenance on products. We assume that all users receive the services detailed in the guidelines.

Whilst some products have a well-defined regimen, the SILCS diaphragm and microbicide gel are used coitally and oral PrEP daily, the newer products (namely the IVR and injectable ARV) are still in development and regimens as yet unknown. We use expert opinion to parameterise use for these products, defining both as products which require monthly application via a health facility. In a sensitivity analysis, we reduce the health system contacts required for efficacious use of these products.

Distribution Costs

The main cost model takes a health system (provider) perspective and presents the incremental costs of each new prevention product (total costs less costs averted by the introduction of the products). Table S3:4 (at the end of this supplementary file) displays model parameters and sources. Included are fixed provider costs, mass-media costs (at a country level) alongside with initial and refresher training (annually at a third of the initial intensity) at a provider level. (10) (10) (9) (7)(20)(18)(17) Provider training costs were based on personal communication with the female sex worker PrEP rollout in

South Africa and based on actual training provision for the rollout of oral PrEP, as per Table S3:1. Training was held over three days, with around 25 participants from a facility per day comprising of 20 nursing staff and 5 HIV counsellors. Variable costs vary with the number of users and include direct product and associated testing costs, and user counselling costs. In addition to this, following the literature (10, 27), overhead costs are accounted for through the use of a facility mark-up factor which captures direct health facility costs as twice labour costs, alongside a health system cost (half of the facility mark-up) which captures resources spent on upper management and logistics.

It is anticipated that the initial introduction of products would incur large fixed costs relating to training and mass media, whilst later products would not need such a large volume of initial resources. So that the sequence of product introduction does not affect cost-effectiveness estimates, as presented in supplementary material S1, we assume a pool of common, fixed training (\$34.7m) and mass media (\$5m) costs before the introduction of any product. Because we assume that all products in a scenario are brought to market at the same time, fixed costs are divided equally across products introduced in each scenario. When estimating population level costs, the division of fixed costs is weighted proportionately to the number of users in each group, which is described fully in supplementary table S4. To estimate costs for MPTs that do not yet exist, we use cost estimates for presently available injectable and oral contraceptive products to estimate unit costs of compounds and associated health services.(28) These costs would be present if MPTs were either co-formulated or co-provided.

The SILCS diaphragm is assumed to have a 1 year useable life (likely a conservative estimate (10)), whilst gel, oral PrEP and IVR supplies are refreshed after a three month period when a user reports to a facility for HIV and syndromic STI testing alongside a panel of other maintenance tests. This period is based on the South African PrEP guidelines (26), alongside the resource planning of the International Partnership for

Microbicides (IPM), the producer of a leading dapivirine IVR (personal communication). Injectable ARVs are assumed to require monthly engagement with the system to receive new injections. We assume no shipping taxes or customs excises, and take a provider perspective as, in the South African context, the public health system is most likely to finance the rollout of new prevention technologies.

Oral PrEP is estimated to have an annual cost of \$75 (\$70-\$130), with the unit price taken from costing studies and the Clinton Health Access Initiative ceiling price list (49)(43). The SILCS diaphragm is estimated to cost \$5.19 per diaphragm, whilst gel use is estimated at 4ml per dose in an average of two sex acts per week.(29) Assuming 10% wastage for gels, users require seven 70ml tubes of gel per year at US\$3.69 per tube, with an annual gel cost of US\$25.83 (CONRAD, personal communication). Due to their continued development, unit costs for the injectable ARV are not available. One option, used in other studies have assumed similarities in costs to oral PrEP.(1, 30) We explore a range of injectable costs through a sensitivity analysis, but base our mean product cost on that of the vaginal ring, however note that the higher requirements for health system utilisation of an injectable regimen will likely make this product cost more per person per year.

Cost parameters were taken from peer-reviewed sources where possible, with programmatic experts approached to inform assumptions around new products or unknown factors. All costs are presented in 2015 US Dollars (US\$). Non-tradable goods (training and labour costs for example) were inflated using local currency inflation rates, whilst tradable goods (product costs) were inflated using the US\$ inflation rate.

Unwanted or mistimed pregnancies

Where new HIV prevention products offer contraceptive properties in addition to HIV protection, secondary benefits will accrue. We calculate the additional impact of contraceptive properties among women who are not currently using modern

contraceptives through estimating the number of pregnancies averted by product use. The likelihood of getting pregnant without using contraception was estimated as 40% based on DHS data for South Africa.(11) As in Lepine et al 2013 (10), we define the added benefit of new products as the difference between this figure and the annual likelihood of conception when using a new product multiplied by the number of women using each product. For all products, we parameterise contraceptive aspects of the model using the characteristics of the SILCS diaphragm. The annual probability of pregnancy while using the SILCS diaphragm with a contraceptive gel is 17.8% for typical use and 13.7% for perfect use per year.(31)

Table S3:1 Included costs

Provision	1 st year by month				
	Initiation		Maintenance		
	0	1	4	7	10
HIV Test	x	x	x	x	x
Creatinine clearance and chemistry panel	x	x	x	x	x
Urine pregnancy test	x				
Syphilis test (RPR)	x				
Syndromic STI screening	x	x	x	x	x
Address side effects		x	x	x	x
Adherence counselling		x	x	x	x
Product distribution	x	x	x	x	x
Behavioural sexual risk reduction counselling	x	x	x	x	x

*Injectables are assumed to be delivered monthly not quarterly, though the suite of testing is only assumed to be completed quarterly as per current PrEP guidelines

Adapted from South Africa PrEP guidelines, May 2016 Final Draft

Averted DALYs and costs

The average age of infection was assumed to be 20 among women aged 16-24 and 30 among women aged 25-49 and FSWs and varied in a one-way sensitivity analysis. After the first 3 years of asymptomatic HIV, those with no ART access live 5 years with symptomatic HIV followed by 2 years of AIDS ending in palliative care and death (32). We use estimates of life expectancy for those on ART and those uninfected from a South African cohort.(33) Loss-to-follow up is assumed to be zero, rendering this analysis on the conservative side, however the lower levels of use assumed in the sensitivity analysis could be interpreted as loss to follow up as the impact model used does not consider adherence over time. Standard DALY estimates are used for HIV/AIDS with and without ART taken from the 2010 Global Burden of Disease study.(14) Disease progression and costs averted are estimated separately for the proportion of HIV positive persons receiving ART (assumed to be 71% of HIV positive persons(12), though raised to 80% and 90% in a one-way sensitivity analysis), whilst lifetime treatment costs for HIV positive persons receiving ART are estimated by multiplying expected life expectancy on ART (33) by annual cost estimates of Meyer-Rath et al.(12) and discounting. For those

not accessing ART, we estimate average lifetime HIV/AIDS health care costs using inpatient cost data, varying this in a sensitivity analysis (34).

As per DHS data, we assume that 92% of pregnant women access antenatal care and delivery (11) with visits using 30 minutes of nurse time over four prenatal visits.(35) Our delivery cost estimate is a weighted average of five possible delivery outcomes: healthy child delivery, low birth-weight child, neonatal death, stillbirth and miscarriage. We follow Lepine et al. (10) in estimating costs averted from the prevention of unintended pregnancies by separating unintended births, and mistimed births that occur early but would have occurred in the future. In the 2003 DHS survey, among women who did not want their last child ($n = 1,434$ representing 52% of total women), 49% declare that the last child was unwanted and 51% declare that they would have liked to have this birth in the future(11). We follow Trussell (36) to assume that a mistimed birth would have occurred two years later, and incorporate a 10.5% abortion rate (37) by assuming that abortion amongst wanted pregnancies is zero, whilst the abortion rate among women with mistimed or unwanted births is estimated at 20.2% ($10.5/0.52$).

Sensitivity analysis

We adhere to the ISPOR guidelines for a robust sensitivity analysis, and only apply probabilistic distributions around appropriate parameters.(38) The primary outcome measure used in the sensitivity analysis is product cost per person per year. At this stage we do not take into account sensitivity due to fixed costs, such as staff training or media costs.

From the literature and expert opinion, we derive a reasonable range of uncertainty around each parameter central estimate. Where more than one estimate was found in the literature, we specify upper and lower bounds according to the smallest and greatest values found and use a uniform distribution to sample random draws. Where

parameters are reported in the literature with estimates of statistical uncertainty, e.g. standard errors, these are recorded and an applicable distributional form assigned. Where there is no variation in reported parameters, we use expert opinion to set higher and lower bounds for parameters, and use a uniform distribution. We run a Monte Carlo simulation with 1,000 draws for each aggregated parameter of interest (e.g. cost per person per year). Results are reported with the mean and inter-quartile range for each measure.

Separate PSAs were run on the cost and cost-effectiveness models. We incorporate variation in cost parameters in the cost-effectiveness model one-way sensitivity analysis by using the 25th and 75th percentile cost estimates, and sample a uniform distribution between these quartiles in the PSA to reflect the large degree of uncertainty in their estimation.

Results

The average variable cost per person per year by product is shown in table S3:2. First year costs were higher due to the more intensive initiation period. First year costs ranged from \$281 for gel, adding the SILCs diaphragm only increased costs by \$6. The highest estimated first year costs were for injectables (\$625).

Modelling estimates were sensitive to direct product costs and the number of visits required per year. The higher frequency of visit required for monthly injections increased costs for the injectable ARV substantively, and injectable costs are very sensitive to the frequency of dosage. The remaining four products have a very similar patterns of contact with the health system, and have similar cost estimates. Microbicide gel and SILCS diaphragm (with gel) costs were very sensitive to the number of sex acts per year, as gel use is coitally specific. Fixed costs were mostly driven by assumptions made around the mass media profile for each product which will be variable depending on available resources. There was limited data to base these assumptions on, and the

modelling literature has used a variety of assumptions around mass media strategies, synergies, and potential costs. Bottom up data are available for individual programmatic activities in Malawi and Zambia, however, these were not included in this model due to a) the context specific nature of the costs themselves, and b) the lack of evidence to predict total social marketing spend by population group. Instead, the standardised overhead cost applies to each population across each product.

Table S3:2: Resource use per prevention product visit – first visit and maintenance visits

	First two visits combined (month 0 and month 3)		Maintenance visits	
Product	Nurse time (hours)	Counsellor time (hours)	Nurse time (hours)	Counsellor time (hours)
Oral PrEP	0.5	0.5		0.5
Microbicide	0.5	0.5		0.5
SILCS diaphragm	0.5	0.5		0.5
Vaginal ring	0.5	0.5		0.5
Injectable	0.5	0.5	0.25	0.5

Comparison with other studies

These cost profiles are generally 1.5-3 times greater than other estimates in the literature. Given that the model is parameterised using similar inputs to other studies, it is likely that this increase is driven by the incorporation of full chemistry panels and syndromic STI tests as per South African guidelines – most other models do not include these costs.

Limitations

As with any modelling exercise, this model is a simplification of reality. To make the model operational, we make a number of assumptions around product availability and rollout. Firstly, we assume that products become available across South Africa at the same time, as indicated by assumptions around training in each health facility and mass media costs. In reality there would likely be a smaller-scale pilot phase of rollout.

Depending on how roll-out occurred, it is unclear *a priori* how this would affect these estimates. Secondly, we assume that there are no economies of scale within product rollout, for example assuming that all training sessions are of the same size and are held by each provider individually. We also assume no synergies in rollout across products, for example the use of mass media to promote more than one PrEP delivery system, or the reduction in potential user reticence to use a new product in previous products have been marketed well. Both of these assumptions are likely to make our estimates conservative.

Thirdly, we assume that guidelines around PrEP are adhered to perfectly, though we allow for treatment coverage to be less than 100%, as has been observed. This is likely to reduce effectiveness of products and thus reduce averted costs; the impact of imperfect adherence is also likely to be different across the products considered. We also assume that the published guidelines for oral PrEP among female sex workers in South Africa, so far the only available PrEP guidelines, are applicable for all populations and all products – this is the cause of the similarity in resource use estimates across products. In reality, there is likely to be some variation across products in these factors, however it is unclear before their introduction and guideline publication how, for example, three-monthly HIV testing, might vary across products in reality.

Cost model results

Table S3:3 and Figure S3:1 detail the results of a probabilistic sensitivity analysis on the cost model, alongside the interquartile range of estimates. In this analysis, we only use the first-year cost, which results in a more conservative analysis given the anticipated reduction in costs in later years, particularly due to less intensive training.

Figure S3:1: Average variable costs per product (probabilistic approach)

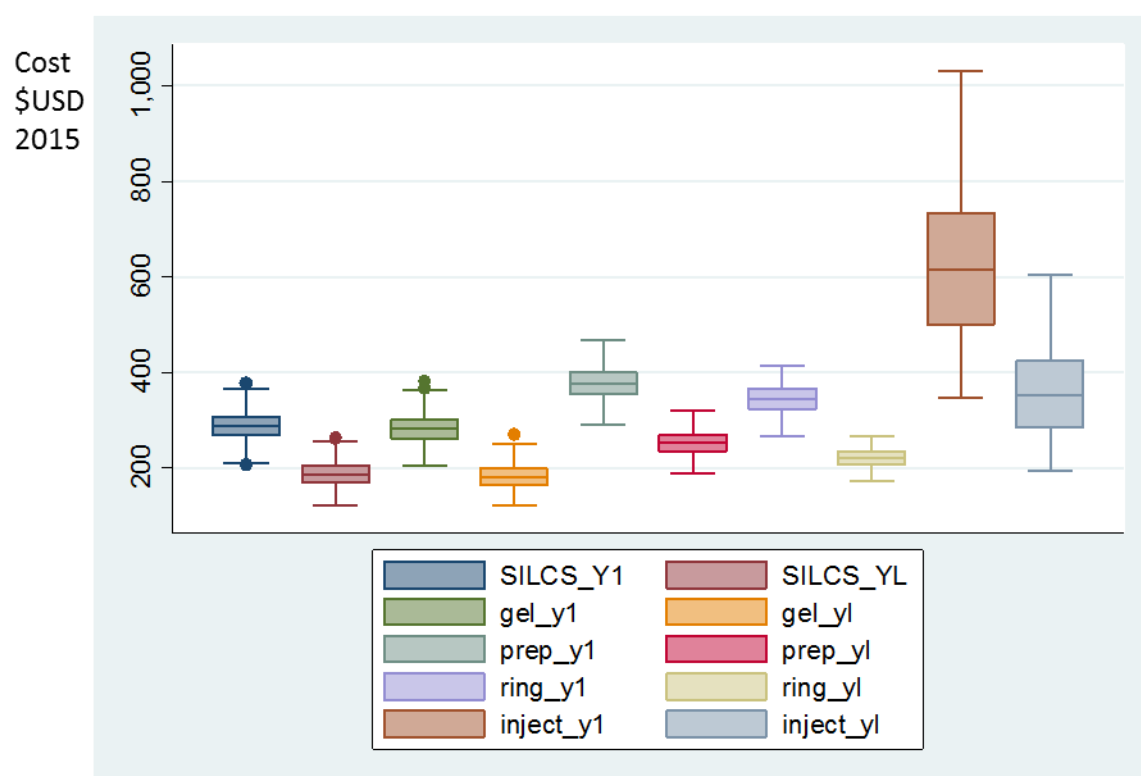


Table S3:3 Annual variable product cost per person per year, first year of introduction

Product	Point estimate	Lower Interval/95%CI	Credible Interval/95%CI	Upper Interval/95%CI	Credible Interval/95%CI
Oral Prep	\$289	\$269		\$309	
Vaginal Ring	\$258	\$243		\$273	
Microbicide Gel	\$212	\$192		\$230	
Injectable	\$438	\$349		\$516	
SILCS Diaphragm and Microbicide Gel	\$217	\$199		\$235	

Table S3:4 Cost model inputs

	Central value (Costs US\$ 2015)	Upper Bound (if available)	Lower Bound (if available)	Source	PSA distribution (if applicable)
Fixed costs					
Number of public sector facilities	3182			(39)	
Training cost per facility	10904			Calculation and (26)	Uniform (+- 25%)
Annual refresher cost per facility	3635			Calculation and (26)	Uniform (+- 25%)
Mass media (total budget)	5000000	5,000,000	1,000,000	(1)	Uniform (+- 25%)
Wage of staff providing products					
Nurse wage per hour	19.11	24	8	(40)	Uniform (+- 25%)
HIV counsellor wage per hour	14.42			(41)	Uniform (+- 25%)
Physician wage per hour	75.09			(15)	Uniform (+- 25%)
Consumables					
HIV test	6.19	6.75	4.67	(42, 43)	Uniform (+- 25%)
Chemistry panel inc. creatinine clearance	33.03	40	30	(42)	Uniform (+- 25%)
Averted costs - Pregnancy					

Pregnancy outcome cost (healthy)	75.6			(44)	Uniform (+- 50%)
Pregnancy outcome cost (Low birth weight)	1570.8			(44)	Uniform (+- 50%)
Pregnancy outcome cost (Neonatal death)	3724.6			(44)	Uniform (+- 50%)
Pregnancy outcome cost (Stillbirth)	75.6			(44)	Uniform (+- 50%)
Pregnancy outcome cost (Miscarriage)	73.1			(44)	Uniform (+- 50%)
Spontaneously aborted pregnancy	36.3			(44)	Uniform (+- 50%)
Pregnancy costs					
Average number of days of work lost due to pregnancy	3			Assumption	
Number of prenatal visits per pregnancy	4			(11)	
Proportion of births that are really unwanted	49%			(11)	
Proportions of unwanted births that are mistimed	51%			(11)	
Years when mistimed births would occur	2			(45)	
Abortion rate	10.50%			(46)	

Abortion rate among unintended pregnancies	20.20%			(11)	
Delivery rate among unintended pregnancies	79.80%			(11)	
Number of visits for abortion (pre-act)	3			(47)	
% of women receiving antenatal care	92%			(11)	
% of women where delivery was assisted by skilled health worker	92%			(11)	
Number of prenatal visits needed when pregnant	4			(11)	
Product-specific costs					
SILCS Diaphragm cost per year	5.19	6	4	Kessel (Personal communication) {Kessel, 2015 #1464}	Uniform (bounds)
Oral PrEP drug cost per year	75	130	70	Assumed using ranges from primary studies: CHAI ceiling price 2015: \$67.20/year (49) South African Investment case: \$75.13(43); CHAI ceiling price 2010 \$75 cited in (50)Walenksy(42) (direct	Uniform (bounds)

				link no longer available). (1)	
Microbicide gel tube cost	3.69	4.5	3	Kessel (Personal communication) {Kessel, 2015 #1464}, Population council (personal communication)	Uniform (bounds)
Intravaginal ring cost	6	7	5	Bodarky, (personal communication){Bodarky , 2015 #1465}	Uniform (bounds)
Injectable cost per injection	5	7	5	Assumption from cost of IPM IVR	Uniform (bounds)
Number of sex acts per year	104	208	20	(29)	Uniform (bounds)
Quantity of gel used per sex (in ml)	4			Kessel (Personal communication) {Kessel, 2015 #1464}	Uniform (bounds)
Clinic visits per year by product					
SILCS diaphragm, microbicide gel, oral PrEP, IVR	4	4	3	(26)	
Injectable ARV	12	12	4	(51)	
Discount rate	0.03			(52)	

Supplementary file S4: Division of fixed costs across populations

To estimate population-level cost-effectiveness, we account for the allocation of programme fixed costs across the three groups differently, depending on the type of cost. We allocate facility-level fixed costs for training across general population groups according to the proportion of general population females in each group. FSW training costs are calculated through multiplying the number of FSW-specific facilities operating in South Africa by estimated training costs per facility. Mass media costs are only allocated to general population groups, proportional to size. Finally, FSW peer-educator and outreach costs are estimated by assuming 12 peer-educators per site working one day per week. Table S3:1 displays these costs as allocated.

Table S4:1 Summary of annual fixed costs by population group

Assumptions	Training	Mass media	Peer educator / outreach costs	Total
Women 15-24	\$12,872,686.84	\$1,855,023.45		\$16,561,101.57
Women 25-49	\$21,824,143.70	\$3,144,976.55		\$28,077,422.00
FSWs	\$1,112,217.70	\$-	\$403,920.00	\$1,574,444.67

Supplementary file S5: HIV infections averted

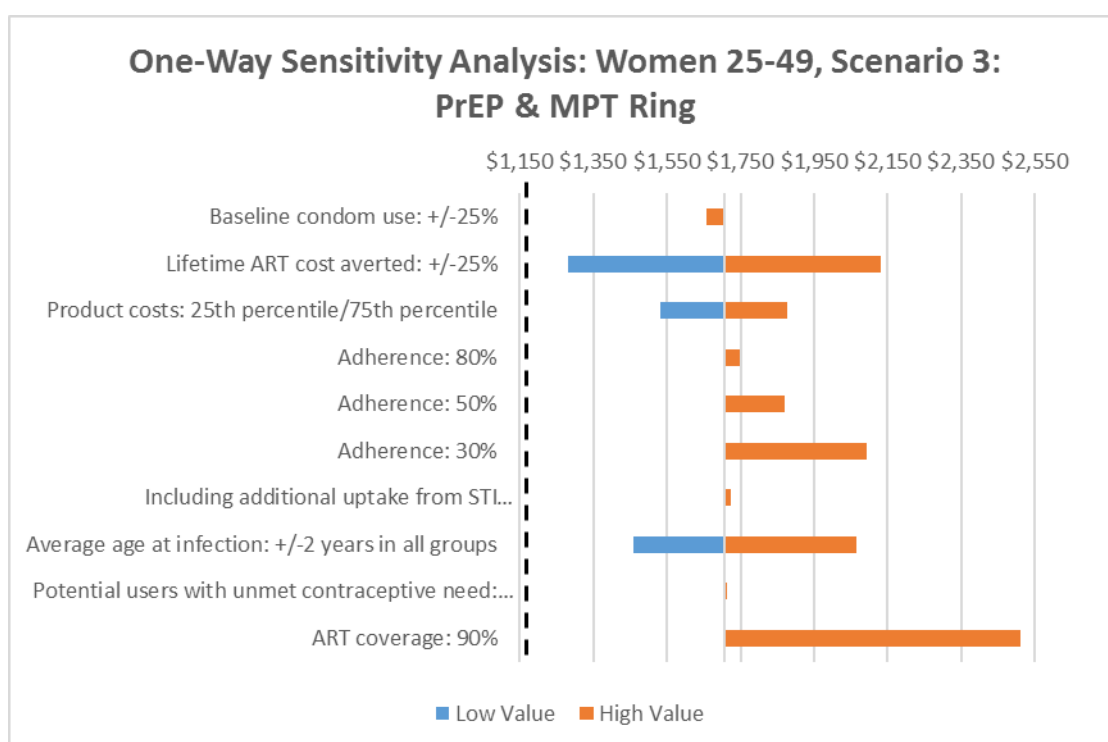
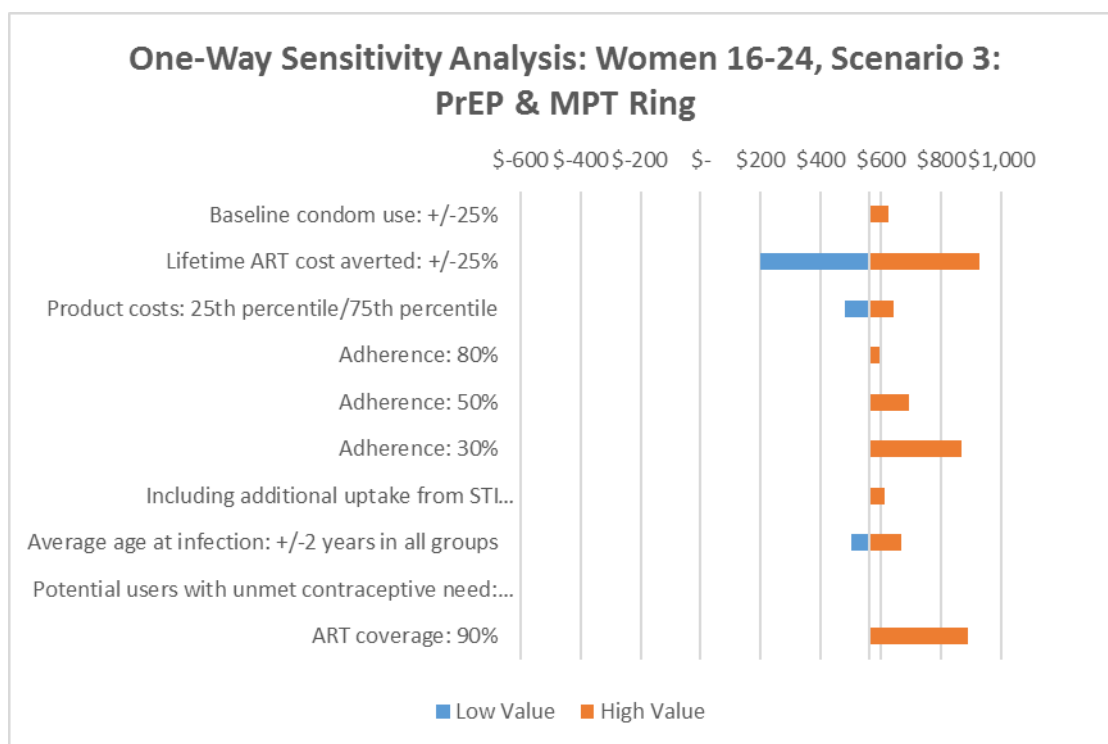
Table S5:1 Total HIV infections averted by scenario

Women 15-24	HIV infections			HIV Infections averted		
Scenario	Low incidence	Central Incidence	High incidence	Low incidence	Central Incidence	High incidence
Counterfactual	69,052	108,266	213,123			
Scenario 1: Oral PrEP with HIV protection only	65,020	101,945	200,680	4,031	6,321	12,443
Scenario 2: Oral PrEP & vaginal ring with HIV protection only	64,238	100,719	198,265	4,814	7,548	14,858
Scenario 3: MPT ring plus oral PrEP	62,234	97,577	192,080	6,818	10,690	21,043
Scenario 4: All five products with HIV protection only	63,911	100,206	197,256	5,141	8,060	15,867
Scenario 5: All five products with multipurpose protection	51,946	81,446	160,327	17,106	26,820	52,796
Women 25+		HIV infections			HIV Infections averted	
Scenario	Low incidence	Central Incidence	High incidence	Low incidence	Central Incidence	High incidence
Counterfactual	69,100	93,285	201,543			
Scenario 1: Oral PrEP with HIV protection only	58,675	79,212	171,137	10,425	14,074	30,406
Scenario 2: Oral PrEP & vaginal ring with HIV protection only	56,993	76,940	166,229	12,108	16,345	35,314
Scenario 3: MPT ring plus oral PrEP	56,747	76,608	165,511	12,354	16,677	36,031
Scenario 4: All five products with HIV protection only	56,310	76,019	164,238	12,790	17,267	37,304

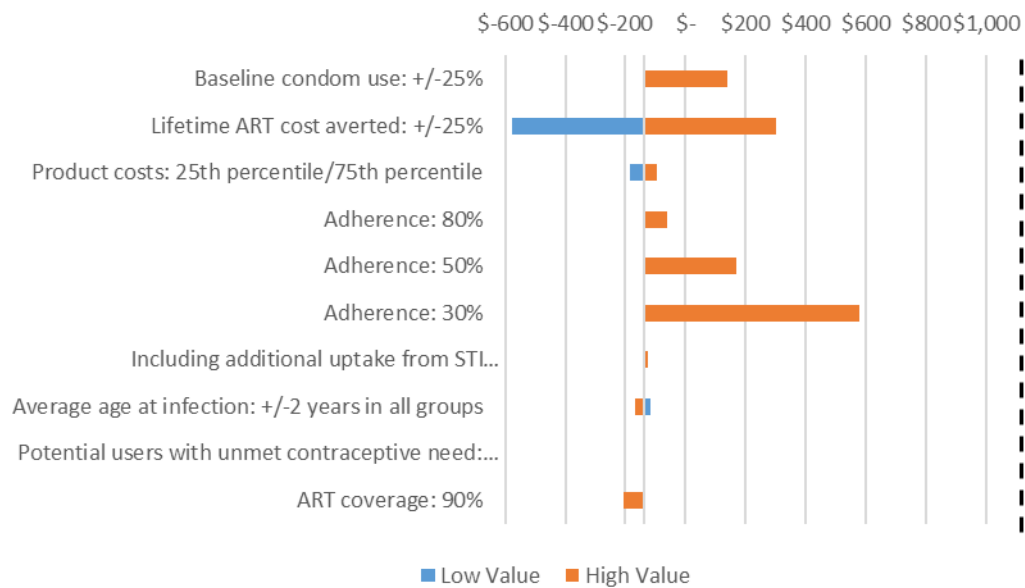
Scenario 5: All five products with multipurpose protection	51,915	70,085	151,418	17,186	23,201	50,125
FSW		HIV infections			HIV Infections averted	
Scenario	Low incidence	Central Incidence	High incidence	Low incidence	Central Incidence	High incidence
Counterfactual	1,026	2,020	3,231			
Scenario 1: Oral PrEP with HIV protection only	877	1,727	2,763	149	293	469
Scenario 2: Oral PrEP & vaginal ring with HIV protection only	737	1,451	2,321	289	569	910
Scenario 3: MPT ring plus oral PrEP	739	1,455	2,329	287	564	903
Scenario 4: All five products with HIV protection only	747	1,471	2,353	279	549	878
Scenario 5: All five products with multipurpose protection	685	1,349	2,158	341	671	1,073

Supplementary file S6: One-way sensitivity analyses

Scenario 2.1: Oral PrEP and MPT ring

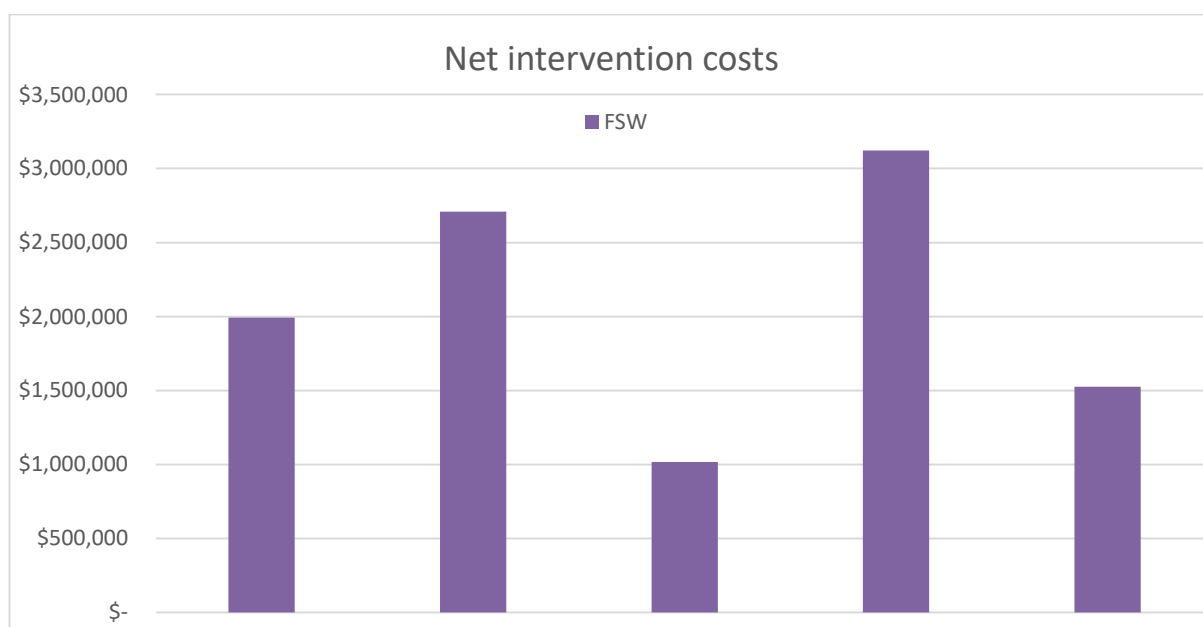
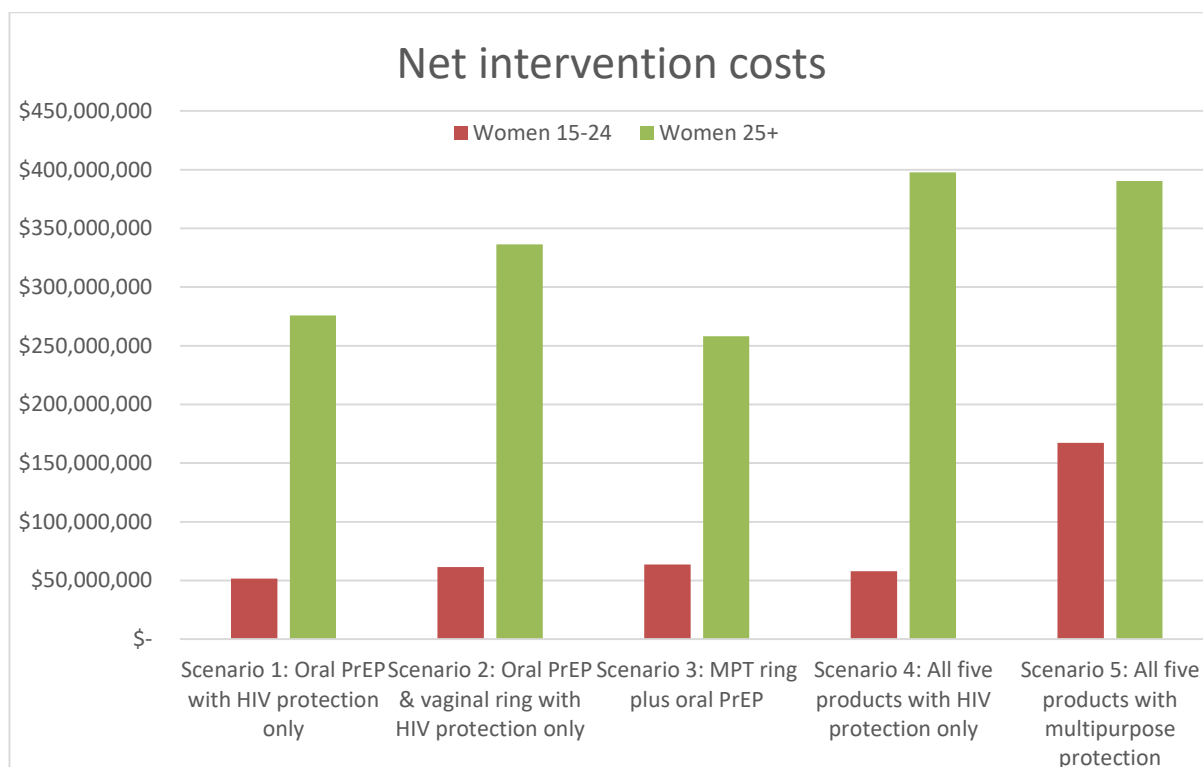


One-Way Sensitivity Analysis: FSW 18-49, Scenario 3: PrEP & MPT Ring



Supplementary file S7: Net intervention costs

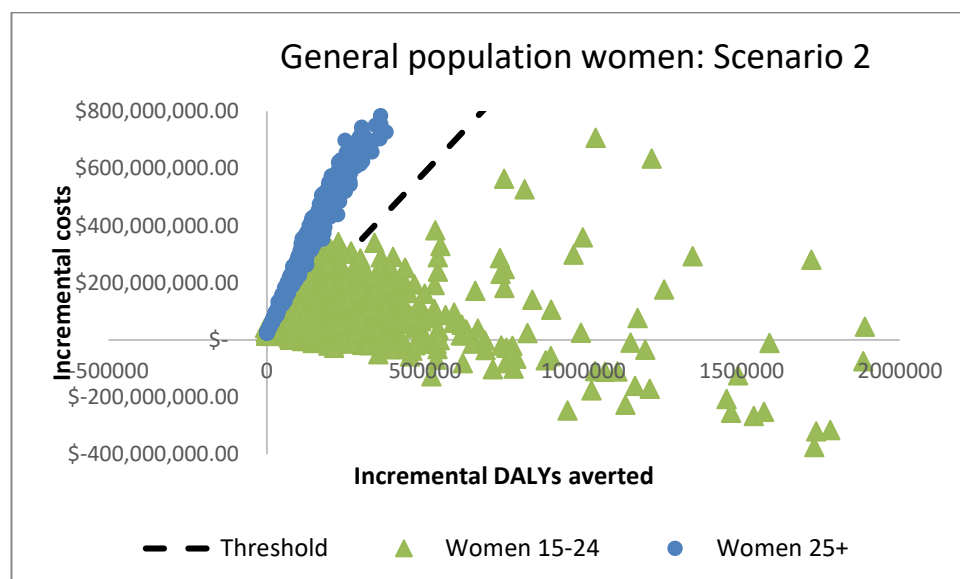
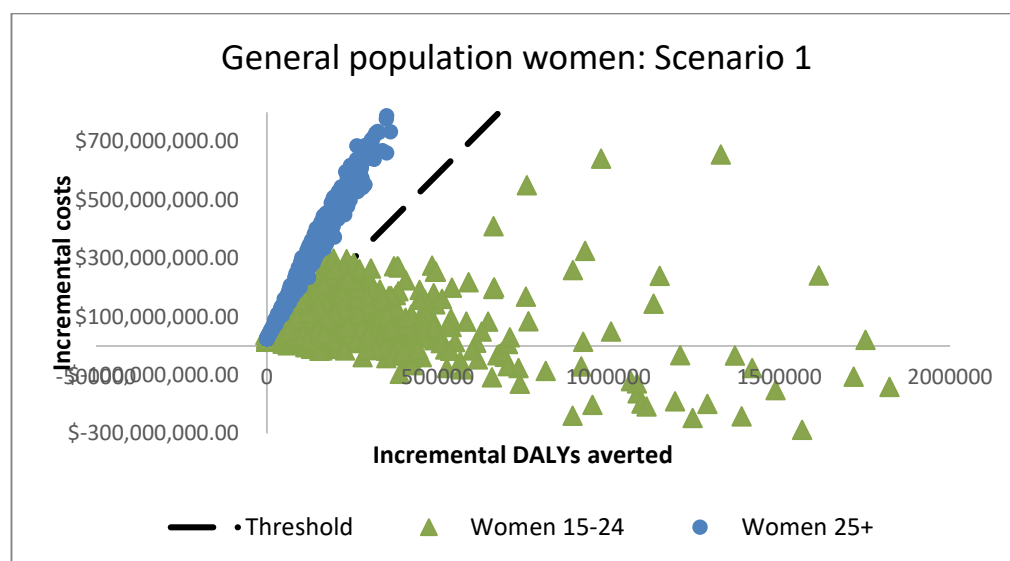
Figure S7:1: Net intervention costs by population

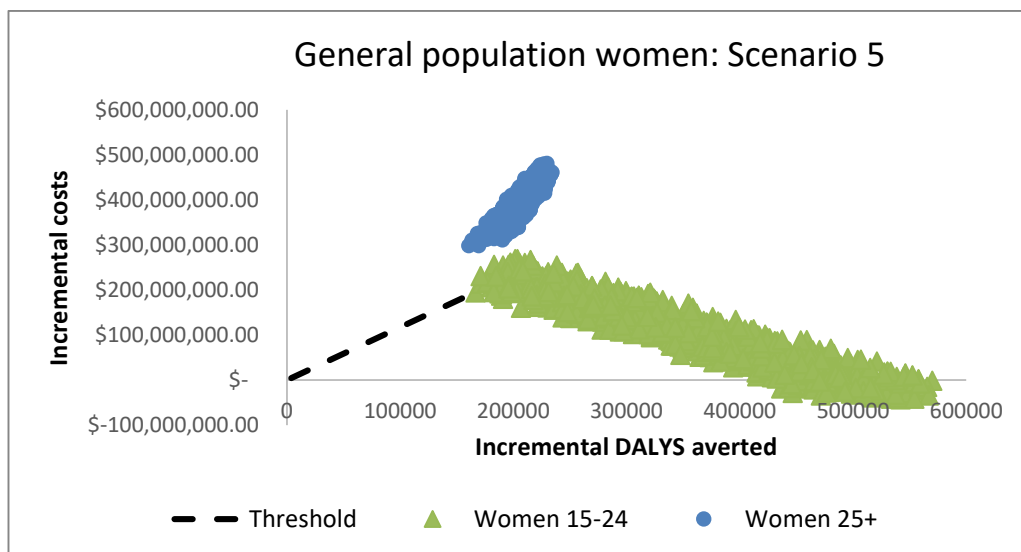
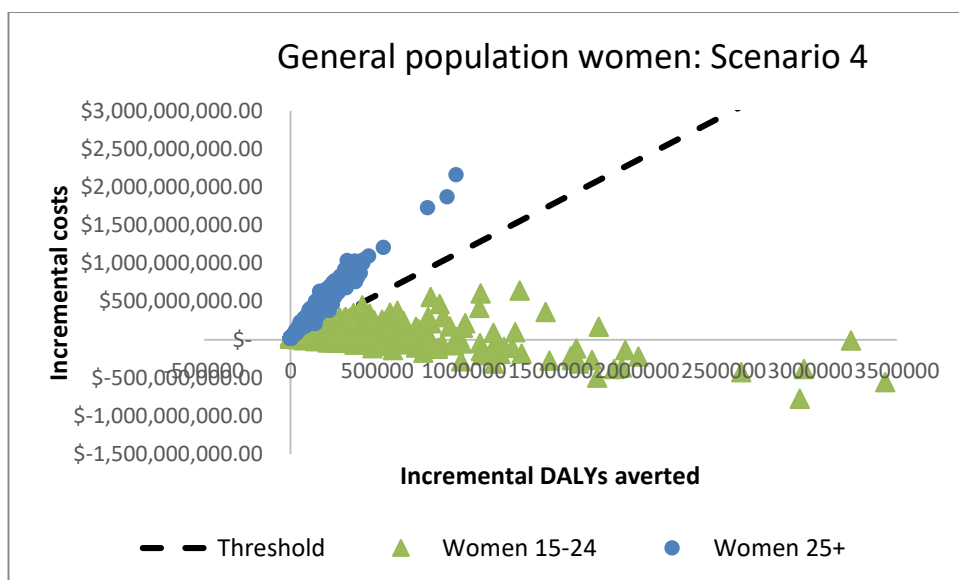
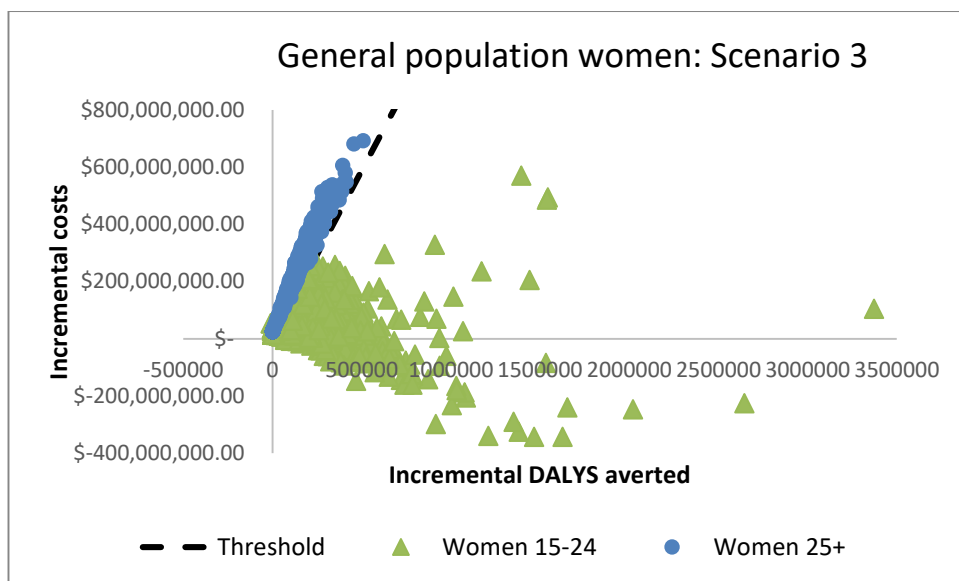


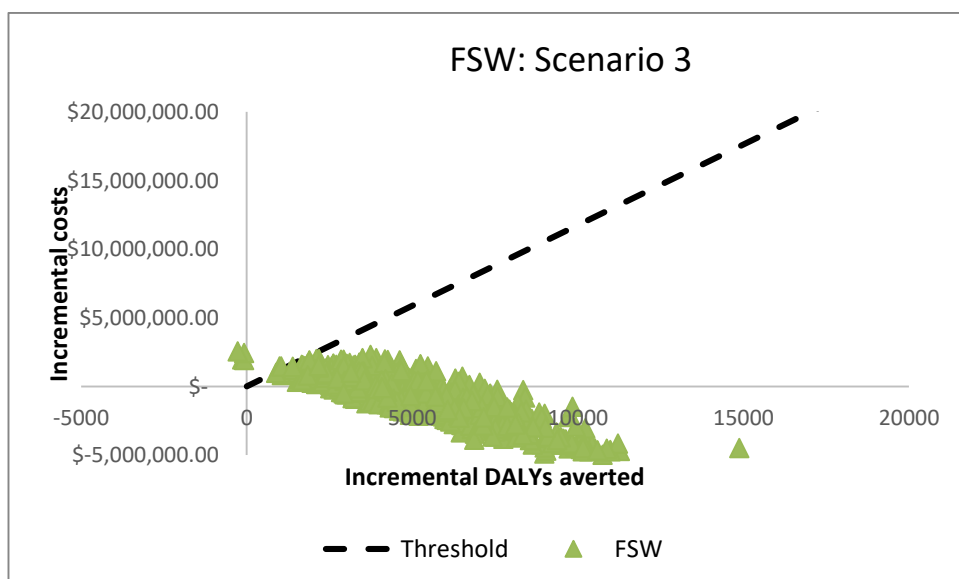
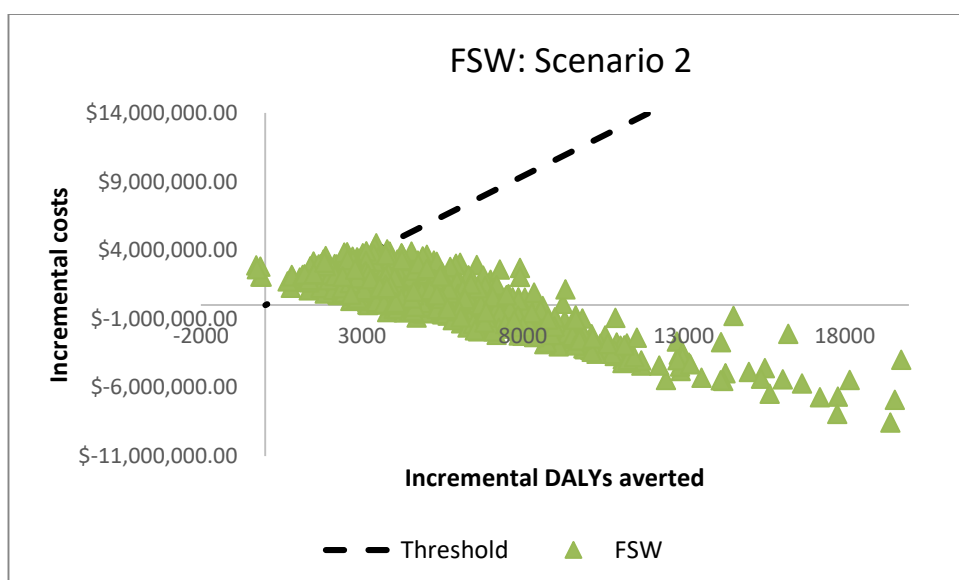
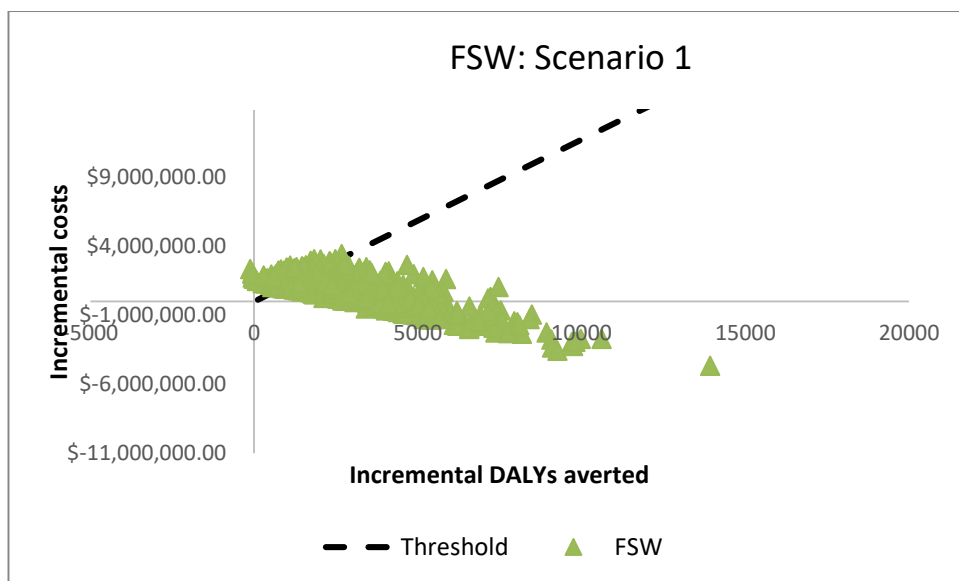
Scenario 1: Oral PrEP with HIV protection only Scenario 2: Oral PrEP & vaginal ring with HIV protection only Scenario 3: MPT ring plus oral PrEP Scenario 4: All five products with HIV protection only Scenario 5: All five products with multipurpose protection

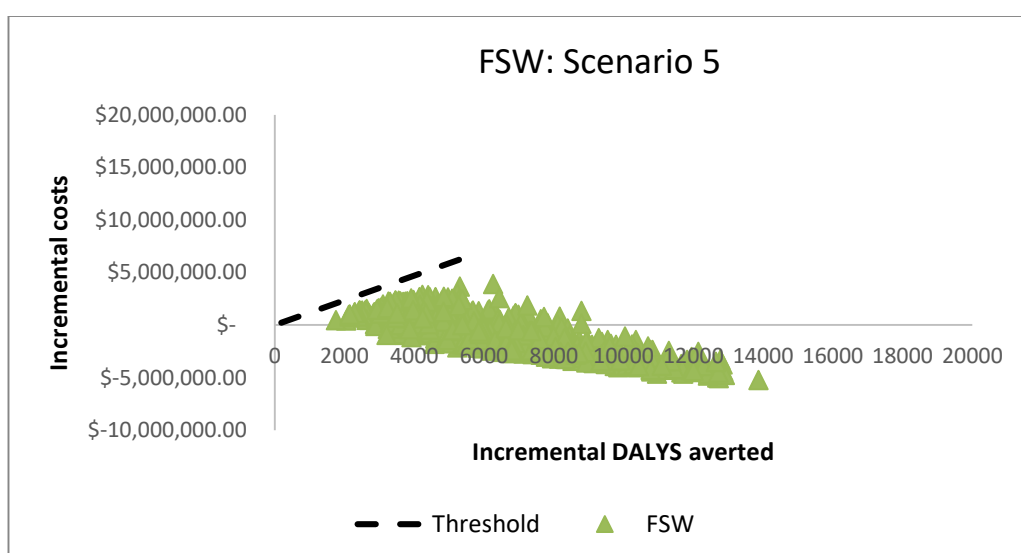
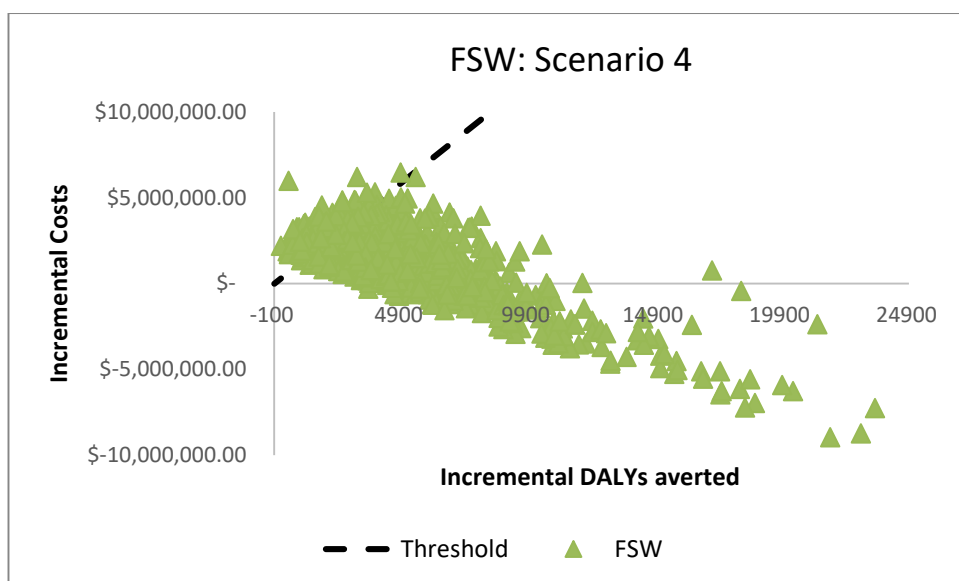
Supplementary file S8: Additional data from probabilistic sensitivity analysis

Below are a series of cost-effectiveness plane plots showing the results of 1000 Monte Carlo simulations carried out for the probabilistic sensitivity analysis. All ICERs are plotted as coloured shapes. Results are plotted on the cost-effectiveness plane and, similarly to Figure 5, when compared to the dashed WTP threshold line, can be interpreted as cost-effective when they lie to the south east. These simulations were also used to generate the CEAC curves in the main analysis.









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Conclusions from paper R2

This paper provides estimates of the short-term impact of a range of candidate MPT products. The finding that MPTs may be cost-effective among younger female groups is important, and reinforces calls from further development of effective MPTs to meet the needs of this group.

This paper also indicates that MPTs may be cost-effective if introduced among FSW groups. Yet, as described in the background section, this model follows the trend of the economic literature and makes assumptions around risk compensation that are not based on empirical data. The next paper, paper R3, uses a DCE to predict the behavioural response of FSWs as a result of PrEP to estimate the influence of economic factors on risk compensation under PrEP use.

Further considerations arising from paper R2

A limitation of the model in paper R2, which was not noted in the accepted version of the paper, is the assumption that unit costs do not vary with scale. In reality, there will likely be some intertemporal dynamic variation between the cost of products and demand: demand for products will depend, in part, on the price of products, whilst prices may be influenced by economies of scale in production. The former may not be such an issue in this case since products are assumed to be provided by the South African Department of Health at no cost to users, though high levels of demand might have a budget impact despite predictions of cost-effectiveness. However, high demand may substantively reduce product unit cost through economies of scale in production; a decrease in unit cost would increase the cost-effectiveness of products, making these results conservative.

National guidelines on long-acting reversible contraception (LARC) in South Africa recommend that condoms are used alongside other contraceptive methods for “dual

protection purposes and enhanced protection from pregnancy”⁶. In the DCE, condom-using participants who chose new products were asked whether they would use them alongside or in place of condoms, with 49% indicating engagement in co-use (implying 51% condom substitution). If MPT users were to adhere to national guidelines, using condoms with hormonal MPT products, they would be more cost-effective than estimated here, since overall protection would be higher (increasing the final summation in equation (2)).

In addition, the model only considers two health outcomes: HIV infection and unintended pregnancy. It therefore does not consider the direct impact of other STIs, alongside any indirect impact of increasing individual susceptibility to HIV acquisition. Not accounting for such negative externalities means that the cost-effectiveness estimates of this model are lower (more favourable) than if STIs were considered. The DALY disability weights for common sequela associated with the three STIs included in the Global Burden of Disease Study (chlamydia, syphilis, gonorrhoea)⁴⁶ are lower than those associated with HIV infection, however without explicitly modelling these we are not able to comment on how cost-effectiveness estimates may change.

Although this paper assesses cost-effectiveness, it does not consider the potential budgetary impact of introducing interventions. If MPTs are introduced to large populations – such as the general population groups modelled here – the overall impact on the health budget may make them unaffordable. Though beyond the scope of this paper, a rigorous, policy-focused budget analysis is required before recommending the introduction of MPT products.

⁶ Page 72, National Contraception Clinical Guidelines, Department of Health, Republic of South Africa. <https://www.mm3admin.co.za/documents/docmanager/3c53e82b-24f2-49e1-b997-5a35803be10a/00037761.pdf>.

Finally, we conducted a threshold analysis presented in table 6 to explore the product unit costs above which we would estimate that products are not cost-effective. Results indicate that the SILCS diaphragm could sustain the largest price increase and remain cost-effective (*ceteris paribus*) with a four-fold price increase. Oral PrEP could sustain the smallest price increase (36%) when introduced in isolation. Results suggest a degree of flexibility in the unit cost of products which are yet to be introduced (i.e. all except oral PrEP) before the model indicates that they will become cost-effective; this is important since cost assumptions for these products are highly uncertain when made prior to introduction and therefore robust programmatic costing.

Table 6: Threshold analysis of scenarios among women aged 15-24, central incidence

	PrEP**	Ring	SILCS	Gel	Injectable
Base-case price	\$ 75.13	\$ 7.00	\$ 5.19	\$ 3.69	\$ 7.00
Threshold price by scenario (holding other prices constant)	S1 (PrEP) \$ 95.53				
	S2 (PrEP) \$ 102.24	S2 (ring) \$ 15.84			
	S3 (PrEP) \$ 100.58	S3 (ring) \$ 15.47			
	S4 (PrEP) \$ 215.65	S4 (ring) \$ 20.70	S4 (SILCS) \$ 22.26	S4 (gel) \$ 11.85	S4 (inject) \$ 12.76
	S5 (PrEP) \$ 288.24	S5 (ring) \$ 18.25	S5 (SILCS) \$ 24.13	S5 (gel) \$ 8.86	S5 (inject) \$ 15.80

**Annual price, other prices reflect unit product cost

Chapter 8: Paper R3 – The effect of HIV prevention products on the supply of condomless commercial sex amongst female sex workers in South Africa

Overview of paper R3

Chapter 3 detailed how existing mathematical models have incorporated assumptions of risk compensation. This paper presents the results of a second DCE, carried out solely among FSWs, with the aim of estimating the impact of introducing an effective HIV prevention product on the choices of FSWs. The paper uses a repeated discrete choice experiment with a difference in framing to quantify substitution from condoms under PrEP, and explore changes in act pricing. Results are analysed using MNL and MMNL models, and preference heterogeneity is considered through the incorporation of random parameters and interaction terms incorporating participant characteristics.

The paper is written in a different style from others in this thesis as it is currently under submission to *Health Economics*, which has different expectations of terminology, structure, and referencing style compared to public health or disease-specific journals. This paper meets thesis objective 3, to assess whether HIV prevention products will change FSW preferences for the supply of condomless commercial sex. It also contributes to objective 4, to explore if changing incentives in sex work could substantially impact the impact of HIV prevention products, by producing behavioural predictions which are incorporated into the mathematical model in paper R4 which immediately follows this paper.



RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Matthew Quaife
Principal Supervisor	Fern Terris-Prestholt
Thesis Title	Using stated preferences to estimate the impact of new HIV prevention products in South Africa

If the Research Paper has previously been published please complete Section B. If not please move to Section C

SECTION B – Paper already published

Where was the work published?	
When was the work published?	
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	
Have you retained the copyright for the work?*	Was the work subject to academic peer review?

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Journal of Health Economics
Please list the paper's authors in the intended authorship order:	Matthew Quaife, Shanthi Manan, Peter Vickerman, Robin Eakle, Maria Cabrera, Sinead Delany-Moretlwe, Fern Terris-Prestholt
Stage of publication	Submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Conceptualised study, led design & analysis, wrote first draft and incorporated co-author comments.
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Student Signature: _____

Date: 17/7/17

Supervisor Signature: _____

Date: 17/7/17

The impact of effective HIV prevention products on the supply of condomless commercial sex amongst female sex workers in South Africa

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Abstract

Evidence suggests that economic factors play an important role in commercial sex work, in particular that condomless sex commands a price premium relative to condom protected sex. This paper explores whether the use of an HIV prevention product, described as 100% effective in preventing HIV, could change the price and quantity of condomless commercial sex supplied. We collected stated preference data from 122 HIV negative female sex workers (FSWs) in urban South Africa, using a repeated choice experiment to simulate the impact of using this product on prevention choices. Results suggest that the price premium for condomless sex would decrease by 73% with the use of this product. The price of an act does not significantly affect choices without protection, but strongly influences choices where full HIV protection is an option. The utility offered by condoms is reduced by around 15% under product use. Because some HIV prevention products do not protect against other STIs or pregnancy, the unintended consequences of introducing new HIV prevention products should be closely monitored,

whilst users should not face stigma or blame for reacting rationally to exogenous changes to market conditions.

Acknowledgements

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Key words: Condom differential, HIV prevention, economics of sex work, risk compensation, South Africa

Introduction

Women engaged in commercial sex, or female sex workers (FSWs), face daily risks of HIV acquisition[1], not least in urban South Africa where HIV prevalence among FSWs is estimated to be as high as 72% in some cities[2]. FSWs face different choices and incentives from other high-risk populations, because, in addition to navigating the complexities of sexual and personal risk in non-commercial sexual relationships, economic and social inequalities mean that FSWs often face strong competition from FSW colleagues, client resistance to condom use, and threats and use of violence from clients and police[3-6]. A growing topic for economic research, analyses have sought to explain entry into and persistence of the industry[7-9], the intensive margin of risk/benefit trade-offs[10, 11], and vulnerabilities faced by FSWs from broader economic forces[12, 13].

Financial incentives in sex work may directly affect the HIV, STI, and pregnancy risk FSWs bear. For example, econometric work has estimated a price premium for condomless sex relative to protected sex, referred to in the literature as the condom differential. Anecdotal evidence of this differential (e.g. [6]) was first empirically estimated by Rao[10] who found that Indian FSWs who used condoms consistently faced income losses of up to 79% as compared to colleagues not using condoms, whilst further econometric evidence has estimated price premia in different contexts between 7% (Belgium and the Netherlands) and 81% (Bangladesh)[10-12, 14-17]. In many circumstances, FSWs are highly dependent on sex work to support themselves and their families[18], and therefore may be at heightened risk when offered more money for unprotected sex.

The HIV prevention landscape has evolved considerably in recent years, not least due to emerging evidence that antiretroviral (ARV) drugs can be used for HIV prevention. Pre-exposure prophylaxis (PrEP) has been shown to offer a high degree of protection when

used by HIV-negative persons in different contexts and populations worldwide[19]. In 2015 the World Health Organisation (WHO) recommended oral PrEP to be used in groups at high risk of HIV acquisition[20]. By implementing national guidelines for the provision of PrEP among FSWs in 2016, South Africa became one of the first countries worldwide to offer ARV-based prevention to any group[21]. In these early stages of PrEP implementation, and with impending new products in the development pipeline in mind, it is critical that we fully understand the impact that effective products might have on potential users' behaviours, specifically to understand potential unintended consequences associated with sustained alternate prevention product use. Such risk compensation cannot be identified by standard comparisons in placebo-controlled trials[22].

We hypothesise that the introduction of a fully effective HIV prevention product will affect the supply of protected and condomless sex because an HIV negative user will bear less risk from engaging in condomless sex. Such a product does not exist, but this provides a useful hypothetical experiment to analyse the perspectives of FSWs. According to the theory of compensating differentials, this would result in both a) an increase in the quantity of condomless sex supplied, and b) a decrease in the price premium for condomless sex. To empirically test this, we interviewed 203 FSWs in Ekurhuleni Municipality, in the urban periphery of Johannesburg, South Africa. We used stated preference methods, a repeated discrete choice experiment (DCE) presented with and without framing of alternate HIV protection, to estimate the effect of hypothetical product use on FSW preferences for condom, price, and client characteristics. Stated preference methods are used frequently in health[23], transport[24, 25] and environmental economics[26], offering a flexible and theoretically robust approach to eliciting preferences towards products and situations that do not yet exist[27]. Although their hypothetical nature means that stated and revealed preferences may not be

perfectly concordant, empirical research in health has shown relatively small levels of hypothetical bias and reasonable external validity[28-30].

When asked to respond as if using a hypothetical, fully effective HIV prevention product, the utility provided to respondents by condom use was diminished by 15%. We find that when given the choice, the use of a 100% effective alternate HIV prevention product will reduce the price premium for condomless sex by 73%, and simulations indicate that the quantity of condomless sex supplied will more than double. The price of an act does not significantly affect choices without protection, but strongly influences choices under full HIV protection.

This paper makes two contributions to the economic literature on sex work and HIV prevention, and provides new insights into a critical population in the country with the world's largest HIV burden. First, to date a body of economic work exists which explores the nature and challenges of sex work, yet no research has looked at the potential impact of new prevention products on the incentives, risks and pressures that FSWs face. Secondly, despite a high estimated prevalence among a national population of 130,000 FSWs[31], to date this is the only published piece of economic work among South African FSWs.

Theoretical model

The following model is an extension of that devised by Gertler, Shah and Bertozzi[11], the first paper to formalise the FSW/client relationship in a partial equilibrium framework. First, we describe their model which considers the market where condoms are the only way of preventing HIV transmission, before extending it to consider the effect of a new prevention product.

FSW and client utility payoffs

Take a client's willingness to pay (utility) for sex to be V , whilst his maximum willingness to pay to not use a condom (disutility) is β . Then:

$$Y_{condom}^{client} = V - \beta - P^c$$

Where Y_{condom}^{client} is a client's utility payoff from condom protected sex with a FSW, and P^c the price he pays her for protected sex. Considering his utility payoff from unprotected sex, the β element is dropped and his payoff function becomes:

$$Y_{nocondom}^{client} = V - P^{nc}$$

Where $Y_{nocondom}^{client}$ is a client's utility payoff from unprotected sex with a FSW, and P^{nc} is the price he pays her for unprotected sex.

The utility payoffs for FSWs are:

$$Y_{condom}^{FSW} = P^c$$

And:

$$Y_{nocondom}^{FSW} = P^{nc} - \gamma - W$$

Thus FSW utility payoffs depend on the amount a client pays. However, when she engages in unprotected sex, she suffers a disutility from exposing herself to risk (from any source), discomfort, or other negative attributes of unprotected sex. Furthermore,

the sex-worker can expect to receive W from the next-best use of her time. Note that this model implicitly assumes the opportunity cost of a client's next best use of time is zero.

We assume that clients and FSWs have a choice whether to engage in any type of sex, though allow for differences in bargaining power between the two groups. The model suggests that a FSW will supply unprotected sex if both she and the client agree not to use a condom. For FSWs, this will occur when the marginal revenue she receives from unprotected sex ($P^{nc} - P^c$) is greater than or equal to her disutility from not using a condom. For clients, this will occur when his marginal cost of not using a condom ($P^{nc} - P^c$) is less than his disutility from condom use. Therefore, two conditions must hold for unprotected sex to occur:

$$\beta > \gamma$$

And:

$$V > (W + \gamma)$$

In other words, that the maximum a client is willing to pay not to use a condom is greater than the maximum a FSW is willing to accept to take the risk; and that the client's maximum willingness to pay for sex is greater than a FSW's costs associated in non-condom sex.

We consider the effect of PrEP on client and FSW payoffs. First, we assume that the FSW's disutility from supplying unprotected sex declines. We define a new parameter, η , that represents this change, so that her payoff from non-condom use is now:

$$Y_{nocondom}^{FSW} = P^{nc} - (\gamma - \eta)$$

Similarly, we assume that male clients' utility from non-condom sex increases by the extent to which a client values HIV protection (which is now provided by PrEP). We represent the clients' utility gain from PrEP by ξ so that his payoff from non-condom use is now:

$$Y_{nocondom}^{client} = V + \xi + P^{nc}$$

Payoffs from condom use have not changed, so we retain the equilibrium price of unprotected sex from Gertler, Shah, and Bertozzi[11]:

$$P^C = (1 - \alpha)(V - \beta) + \alpha W$$

To find the new equilibrium price for non-condom use with PrEP, we maximise: $(V + \xi - P^{nc})^\alpha (P^{nc} - \gamma - W)^{(1-\alpha)}$ where α represents the client's bargaining power, and $(1 - \alpha)$ FSW bargaining power. We obtain:

$$P^{nc} = (1 - \alpha)(V + \xi) + \alpha(W + \gamma)$$

Then, by subtracting $P^{nc} - P^C$, we obtain the price differential between protected and unprotected sex:

$$P^{nc} - P^C = (1 - \alpha)(\beta + \xi) + \alpha(\gamma - \eta)$$

We can then compare the price premium for non-condom use with PrEP to that without PrEP:

$$Prem^{PrEP} - Prem^{Orig} = (1 - \alpha)\xi - \alpha\eta$$

The impact of PrEP on the price premium for non-condom use therefore depends on the relative bargaining weights of the FSW and client, and the amount of utility the client and the sex worker each gain through the use of PrEP. The premium will decline if the following condition holds:

$$\frac{1 - \alpha}{\alpha} < \frac{\eta}{\xi} \quad (1)$$

And rise if the opposite inequality holds.

The following pair of assumptions would generate a decline in the price premium under PrEP:

- (i) The client's bargaining power is greater than the FSW's: $\alpha > 1 - \alpha$
- (ii) The FSW gains more utility from PrEP than the client: $\eta > \xi$

Under these two assumptions, the left hand side of condition (1) is less than 1, whilst the right hand side is greater than 1, so the inequality is always satisfied.

Empirical methods

Study overview

A respondent-driven sampling (RDS) method[32] was used to recruit 203 FSWs in Ekurhuleni Municipality, Gauteng Province. Peer educators were used to locate sex work hotspots and 12 were asked to act as seeds to start RDS chains in different areas (i.e. women working in brothels, hotels or on the street). Seeds were invited to complete the survey and received ZAR 50 (USD \$3.50) compensation for their time before they were given four coupons containing study information to distribute to other FSWs. When each referred FSW attended for an interview, their peer recruiter received a small incentive in the form of a ZAR 20 (USD \$1.40) voucher.

The DCE was designed to elicit FSW preferences towards clients and sex act characteristics. To estimate the impact of a new, 100% effective prevention product on choices, the same ten DCE tasks were presented twice to HIV negative FSWs, firstly with no framing: *"You have the choice between providing services to one of two clients. Which would you prefer?"* prior to a comprehensive description of a range of potential products to respondents. Then, the choice tasks were presented again with a protected framing: *"Now I would like you to choose between 10 more sets of clients, but this time I would like you to make your choices imagining you were using a product which prevented you from getting infected with HIV. This means that there would be no risk of getting HIV from any client, whether or not you use a condom. Which would you prefer?"*

Because respondents answered the same choice tasks twice (with different frames), we were able to test whether different choice task framings had a causal impact on FSW choices. Interviewers were experienced in sexual history surveying, and were thoroughly trained and tested on their explanation of products and the DCE. In a separate DCE carried out in the same sample, preferences for product characteristics were consistent with prior expectations, demonstrating participant understanding of the protective benefits of products[33, 34]⁷.

The study was reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee (HREC) and the Research Ethics Committee at the London School of Hygiene and Tropical Medicine. All participation in the DCE, alongside supporting qualitative studies, was voluntary and subject to completion of written informed consent. The background survey asked several questions which led to a number of disclosures of distressing events, and a comprehensive distress protocol ensured that participants who disclosed these were referred to named persons at local clinics and NGOs.

Questionnaire

Selection of attributes and levels

The development of the DCE tasks was primarily based on thematic analysis of four focus group discussions. These were carried out with 52 self-reported active FSW participants recruited through convenience sampling, with the assistance of FSW peer-educators through a local non-governmental organisation. Qualitative analysis (presented elsewhere[35]⁸) generated a long list of potential DCE attributes, supplemented by key themes emerging from a scoping literature review. Final attributes and pictorial representations of choice tasks were then chosen through discussions with FSWs, peer

⁷ Chapter 6 of this thesis

⁸ Appendix X of this thesis

educators, the FSW community advisory board at the Wits RHI, and input from UK and South African experts in DCE methods. Table 1 presents the final list of attributes and their levels, alongside the hypothesised direction of impact for each (positive or negative impact on utility). For example, we expect the act price to have a positive coefficient and increase utility, whilst providing services to clients perceived to have an STI or HIV is likely to have a negative coefficient as it reduces utility. Figure 1 gives an example of a choice task as presented to respondents. The rest of the questionnaire captured data on a range of factors which may influence risk and pricing decisions such as socio-economic characteristics, commercial and non-commercial sexual history, and exposure to structural risk factors such as intimate partner violence; these are used to explore preference heterogeneity through interaction terms.

Figure 1: Example choice task without protection framing






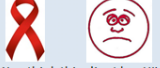
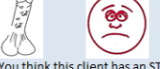
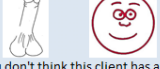


You have the choice between providing services to two clients. Which would you prefer?			
2 of 10	Client A	Client B	Neither
Condom	 Male or Female Condom	 No Condom	Would not provide services to either client
Sex	 Anal sex	 Vaginal sex	
HIV Risk	 You don't think this client has HIV	 You think this client has HIV	
STI Risk	 You think this client has an STI	 You don't think this client has an STI	
Price	 50 Rand	 400 Rand	

Table 1: Attributes and levels

Attribute	Levels	Hypothesised coefficient sign
Condom use	Condom vs. no condom	+
Type of sex	Vaginal sex vs. anal sex	+
Perceived client HIV risk	"You don't think this client has HIV" vs. "You think this client has HIV"	-
Perceived client STI risk	"You think this client has an STI" vs. "You don't think this client has an STI"	-
Price for sex	R100 (US \$7.03), R200 (US \$14.06), R400 (US \$28.12), R800 (US \$56.24)	+
Task frame	No framing: <i>"You have the choice between providing services to one of two clients. Which would you prefer?"</i> Protection framing: <i>"Now I would like you to choose between 10 more sets of clients, but this time I would like you to make your choices imagining you were using a product which prevented you from getting infected with HIV. This means that there would be no risk of getting HIV from any client, whether or not you use a condom. Which would you prefer?"</i>	

Experimental design

We apply best-practice DCE design methods and use a fractional factorial design to generate the experimental design used in piloting, with pilot data subsequently providing Bayesian priors for the final design[27]. A 10-task, D-efficient unlabelled design was generated using NGENE software [36] with four unconstrained binary attributes (condom, sex, HIV risk, STI risk) and one continuous linear attribute (price). Discussion continues in the literature on the best way to create efficient DCE designs, yet D-efficient designs are increasingly popular due to their computational efficiency and statistical performance[23, 37-39].

Analysis

Multinomial logit (MNL) estimation

Random utility models are used extensively in choice modelling, with the majority of health applications based on the multinomial logit (MNL) model[23, 40]. The MNL is computationally simple to implement, however, requires stringent assumptions

including the absence of taste heterogeneity across respondents alongside restrictive patterns of substitution across alternatives. Nevertheless, the MNL is a useful model with which to explore choice patterns in the data before moving to more advanced estimation methods[27].

Thus, the utility of respondent n for alternative i is given by a deterministic and measurable element $V_{n,i}$ and a stochastic, unobserved element $\varepsilon_{n,i}$:

$$U_{n,i} = V_{n,i} + \varepsilon_{n,i} \quad (1)$$

Assuming that $\varepsilon_{n,i}$ has a type I extreme value distribution with values independently and identically distributed, the probability of choosing alternative i from choice set j is given by:

$$P_{n,i} = \frac{e^{V_{n,i}}}{\sum_{j=1}^J e^{V_{n,i}}} \quad (2)$$

The MNL model is estimated by defining $V_{n,i}$ as a vector of explanatory variables from the DCE design $X'_{n,i}\beta_i$ and maximising a log-likelihood function in relation to β .

Mixed multinomial logit (MMNL) estimation

As described by Hess et al. [41], we estimate a mixed multinomial logit (MMNL) where the parameter vector β is assumed to be randomly distributed rather than fixed, such that $\beta \sim f(\beta, \Omega)$:

$$P_{n,i} = \int_{\beta} P_{n,i}(\beta, x_{n,i}) f(\beta, \Omega) d\beta \quad (3)$$

Where Ω is a parameter vector of the distribution of the elements contained in β .

A restriction of the MMNL model is that the analyst needs to specify which parameters are randomly distributed across agents, as well as the way they are distributed (i.e. according to a normal, lognormal, or uniform distribution). The requirement of these assumptions is generally seen as a small cost for the ability of MMNL specifications to

allow for taste heterogeneity, where preferences are allowed to vary across individuals [27, 41].

To test the effect of the DCE framing we define $\beta_{n,i}$ to include

$$\beta_{n,i} = \alpha_n + \delta_n * HIV\ product\ protection_frame_n \quad (4)$$

Where α_n is a coefficient vector capturing preferences with no framing, *HIV product protection_frame* a binary variable equal to 1 when the HIV product protection framed DCE is being presented, and δ_n a coefficient vector capturing deviations between the two framings. We calculate robust t-ratios to test the divergence of δ elements from zero. All parameters are estimated as random and normally distributed in MMNL estimation to reflect uncertainty in the distribution of their variance, except act price which is estimated with a lognormal distribution. 1000 Halton draws are created to estimate the model.

Willingness to accept condomless sex

Analogous to willingness to pay estimates in the literature, we compute the relative importance of sex-act attributes in monetary terms. For example, assuming a utility function which is linear in parameters, the willingness to accept (WTA) condomless sex can be expressed as the monetary value:

$$w_k = \frac{\beta_k}{\beta_c} \quad (5)$$

Where β_k is the parameter for condom use, and β_c the price parameter. Because β_k and β_c are estimated with uncertainty, we consider the extent to which w_k is uncertain using the Delta method to estimate the standard error of w_k . Assuming that $\hat{\beta}$ is asymptotically distributed such that $\widehat{\beta}_k \xrightarrow{D} N(\beta, \Omega_\beta)$, then, as shown in in Bliemer and Rose [42], the asymptotic standard error of w_k is:

$$se(\widehat{w_k}) = \frac{1}{\beta_c} \sqrt{var(\beta_k) - 2w_k cov(\beta_k, \beta_c) + w_k^2 var(\beta_c)} \quad (6)$$

We use the Delta method to assess the significance of the ratio of condom use and price parameters (the condom differential) in the unframed DCE, the HIV product protection framed DCE, and to test whether the ratio z_k is significantly different from zero:

$$z_k = \frac{\beta_k^{prep} / \beta_c^{prep}}{\beta_k^{noprep} / \beta_c^{noprep}} \quad (7)$$

Simulations of behaviour change

We apply predicted probability analysis to simulate the impact of a hypothetical fully effective prevention product on the price and supply of protected and condomless sex. As elsewhere in the health literature[27, 43, 44], we predict the supply response to the product introduction by summing the model coefficients with imputed attribute levels. As best-practice in WTP studies from DCE data, we rescale results for simulation using revealed preference data. We take the absolute price premium as self-reported by FSWs, and reduce it by the factor z_k to generate the new price of condomless sex. We hold all attributes except condom use and price constant across framings, and use MNL model outputs for transparency in simulations, simply substituting $V_{n,i}$ into equation (2).

Results

Characteristics of respondents

Table 2 displays the descriptive statistics from the sample. In total 203 FSWs were interviewed, of whom 81 (40%) self-reported as being HIV positive, all of whom reported currently receiving antiretroviral treatment. The remaining 122 HIV negative respondents completed both DCEs (thus acting as their own counterfactual), and we restrict analysis to this group. Each DCE had ten choice tasks, meaning that we had 20 observations per respondent (10 without protection, and 10 with protection) resulting in 2,440 choice data points. The average age of HIV negative respondents (29.48) was

significantly ($p>0.01$) lower than HIV positive respondents (32.95) and they were significantly less likely to have children ($p>0.01$). In addition, HIV negative FSWs were more likely to make all their income from sex work ($p>0.01$), and to have earned more from sex work in the last week ($p=0.05$). The marriage rate was low at 2% for both HIV positive and negative respondents, though 65% reported being in a relationship. Reported rates of consistent condom use (“always”) with commercial partners are much higher than other FSW surveys in South Africa[2]. Interestingly, HIV positive FSWs report charging significantly more than HIV negative FSWs ($p=0.04$) for protected sex, whilst there is no significant difference for condomless acts. The price premium for unprotected sex among HIV negative FSWs is 1.6 times greater than that of HIV positive sex workers (ZAR 394 (\$30) vs. ZAR 248 (\$19)).

Table 2: Descriptive Statistics

Variable	Whole sample	%/(SD)	HIV Negative (n=122)	%/(SD)	HIV Positive (n=81)	%/(SD)	Difference between HIV positive and negative: t-test p-value
Age	30.87	(6.17)	29.48	(5.72)	32.95	(6.27)	>0.01
Secondary education	155	76%	96.38	79%	59.13	73%	0.44
Married	4.06	2%	2.44	2%	1.62	2%	0.59
In a relationship	132	65%	55	63%	77	68%	0.49
Any children	182	90%	104.92	86%	76.95	95%	>0.01
Always use condoms with clients	196	97%	119	98%	76.95	95%	0.35
Experienced IPV in the last year	70	34%	41.48	34%	29.16	36%	0.75
Used alcohol at last sex	32	16%	18	15%	14	17%	0.15
Low household income (<R5000/month)	125.86	62%	69.54	57%	55.89	69%	0.1
Knows other FSWs engaging in condomless sex	81.2	40%	45.14	37%	35.64	44%	0.28
In debt	78	38%	42.7	35%	34.83	43%	0.26
All income made from sex work	174	86%	108	89%	65.61	81%	>0.01
Amount charged to last client (ZAR)	103.57	(156.70)	114.75	(188.28)	86.73	(88.92)	0.21
Money earned from sex work in last week (ZAR)	1606.45	(1392.34)	1762.54	(1548.29)	1371.36	(1084.49)	0.05
Average price charged for protected sex	83.06	(90.24)	72.38	(72.98)	99.14	(109.88)	0.04
Average price charged for condomless sex	411.16	(355.97)	466.52	(385.13)	347.5	(316.84)	0.28

DCE results

Tables 3 and 4 show results from MNL and MMNL main effects estimation respectively. Both tables show results for the unframed (models 3A and 4A) and protection framed (models 3B and 4B) DCEs. These tables also show the interaction specification of equation 4 (models 3C and 4C), where interaction coefficients represent the difference in preference weights between framings, and where a statistically significant parameter indicates that choices under assumed 100% HIV protection differ from those under no protection.

Results are broadly consistent across MNL and MMNL specifications, and coefficient signs are in line with the theoretical expectations in Table 1. The non-significant price parameters in the unframed models 3A and 4A suggest that FSWs do not choose clients based on price in current practice, but condom use, client characteristics and the type of sex are all important to decision making. However, the significant price parameter in models 3B and 4B suggest that price could strongly influence choices after the introduction of a fully effective prevention product. We test the hypothesis that price will become more important with use by examining the price*protection framing parameter in models 3C and 4C, which show significance at the 95% level and therefore suggests there is strong evidence for an increased influence of price on choices after the introduction of a fully effective product. Additionally, we find that the utility of protected sex is significantly reduced by product use. In the MNL model, we find evidence that the framing of tasks was broadly understood due to the significant reduction in disutility from a client suspected as being HIV positive. However, this is not observed in the MMNL specification suggesting heterogeneity in the effect of framing across respondents. In both models, providing anal sex causes significant disutility in current practice and the extent of this does not appear to change with product introduction.

The MMNL displays lower log-likelihood, AIC and BIC values than the MNL, however, these cannot be directly compared to assess model performance as the randomness introduced by the MMNL will inevitably affect these measures. However, the general consistency across MNL and MMNL specifications is reassuring. The differences that do occur are likely to be because of heterogeneity in preferences among the sample, which is not incorporated by the MNL.

Results suggest that the price premium for unprotected sex will reduce by 73% under full HIV protection, as denoted by the significant condom use and price parameters when interacted with framing. When the significance of the change in the ratio of these two parameters is assessed by the delta method, the change in price premium due to protection is also statistically significant ($p=0.046$).

There is no evidence that HIV protection affects preferences for anal sex, providing services to clients who are suspected of having HIV or an STI, or opting out of providing services to clients. The lack of statistically significant parameters in the unframed DCE WTA ratios, presented in Supplementary Appendix I, may be due to the lack of precision in the price estimate which, in fact, further highlights the relative importance of the price attribute under product use.

Simulations

Since the condomless sex price premium we observe from revealed preference data without a prevention product is ZAR 394 (ZAR 466 – ZAR 72), we predict that the premium will fall to ZAR 107. All else equal, this reduction in the condom differential will lead to an increase in condomless sex by a factor of 2.27 with alternate product use, compared to before introduction. If the premium were to remain constant at ZAR 394, the change in the utility provided by condoms and price indicates that the quantity of condomless sex would increase by a factor of 3.2.

Heterogeneity

We explore observed heterogeneity in our data through specifying interaction effects with several respondent characteristics shown in Table 5. This is a MNL model, as the MMNL model did not successfully converge. The most important finding here is that the impact of the fully protective product does not vary among FSW subgroups (Model 6C), however these null findings may be due to the number of parameters estimated in this model relative to the sample size. Although the effect of the product is consistent across the sample, there is some heterogeneity in preferences for the DCE attributes. Married FSWs value act price significantly less than their unmarried peers across both framings, and there is indicative evidence that recent experience of IPV and knowing other FSWs who engage in condomless sex may increase the influence of price under product introduction.

Table 3: DCE Results – main effects MNL

	Model 3A: No frame MNL			Model 3B: Protection framed MNL			Model 3C: Interacted MNL		
	Coeff.		SE	Coeff.		SE	Coeff.		SE
Price	0.0004		0.0005	0.0012	***	0.0004	0.0004		0.0005
Condom use (base: no condom)									
Condom	4.53	***	0.24	3.69	***	0.22	4.53	***	0.24
Type of sex (base: vaginal)									
Anal	-2.89	***	0.18	-2.98	***	0.17	-0.29	***	0.18
Perceived client HIV risk (base: no risk)									
Think client has HIV	-0.48	***	0.14	-0.24	**	0.13	0.48	***	0.14
Perceived client STI risk (base: no risk)									
Think client has STI	-0.83	***	0.16	-0.64	***	0.15	0.83	***	0.16
Opt-out (no services to either)	1.46	***	0.17	1.00	***	0.14	1.46	***	0.00
Interactions (protection framing x)									
Price							0.0008	***	0.0006
Condom use							-0.84	**	0.33
Anal sex							-0.09		0.25
Client HIV							0.24	**	0.20
Client STI							0.19		0.22
Opt-out							-0.46	**	0.22
Model diagnostics									
Log likelihood	-587.31			-701.79			-		
AIC	1186.62			1415.58			1289.10		
BIC	1216.60			1445.58			2602.21		
N	122			122			2670.51		
							244		

Table 4: DCE Results - main effects MMNL

	Model 4A: No framing MMNL			Model 4B: Protection framed MMNL			Model 4C: Interacted MMNL		
	Coeff.		SE	Coeff.		SE	Coeff.		SE
Price	0.0002		0.0009	0.003	**	0.0009	0.0018	***	0.0006
Condom use (base: no condom)									
Condom	7.46	***	0.56	6.34	***	0.45	6.09	***	0.33
Type of sex (base: vaginal)									
Anal	-1.54	***	0.33	-1.29	***	0.33	-1.66	**	0.29
Perceived client HIV risk (base: no risk)									
Think client has HIV	-0.89	***	0.32	-0.97	***	0.31	-0.69	**	0.21
Perceived client STI risk(base: no risk)									
Think client has STI	-2.33	***	0.41	-1.44	***	0.30	-1.05	***	0.21
Opt-out (no services to either)	-1.58	**	0.46	-1.67	***	0.40	-0.92	**	0.25
Interactions (protection framing x)									
Price							0.0019	**	0.0007
Condom use							-0.86	**	0.42
Anal sex							-0.10		0.35
Client HIV							0.32		0.25
Client STI							0.33		0.28
Opt-out							-0.11		0.30
Distribution parameters (distribution of standard deviation)									
Price	0.0008	***	0.0003	-0.0005		0.0005	-0.0006	**	0.0002
Condom	0.16		0.17	-0.13		0.12	0.12		0.07
Anal	-4.00	***	0.50	-4.85	***	0.61	-2.08	***	0.23
Think client has HIV	0.01		0.21	0.40	*	0.20	0.09		0.13
Think client has STI	1.08	***	0.25	0.51	**	0.21	0.00		0.12
Opt-out (no services to either)	3.11	***	0.37	2.58	***	0.25	2.34	***	0.16
Protection framing x price							0.0019	**	0.0007

Protection framing x condom use			-0.86	0.42
Protection framing x anal sex			-0.10	0.35
Protection framing x client HIV			0.32	0.25
Protection framing x client STI			0.33	0.28
Protection framing x opt-out			-0.73 ***	0.15
Model diagnostics				
Log likelihood	-456.76	-538.05	-1058.664	
AIC	937.5	1100.1	2165.33	
BIC	997.4	1160.1	2301.93	
N	122	122	244	

Table 5: Heterogeneity in preferences - interaction effects

	Model 6A: No framing MNL			Model 6B: Protection framed MNL			Model 6C: Interacted MNL		
	Coeff.		SE	Coeff.		SE	Coeff.		SE
Price	-0.0005		0.0007	-0.0011		0.0006	-0.0005		0.0007
Condom use (base: no condom)									
Condom	4.39	***	0.29	3.80	***	0.28	4.39		0.29
Type of sex (base: vaginal)									
Anal	-2.92	***	0.18	-3.05	***	0.18	-2.92		0.18
Perceived client HIV risk (base: no risk)									
Think client has HIV	-0.49	***	0.14	-0.28	***	0.14	-0.49		0.14
Perceived client STI risk (base: no risk)									
Think client has STI	-0.87	***	0.17	-0.75	***	0.15	-0.87		0.17
Opt-out (no services to either)	1.43	***	0.17	0.92	***	0.14	1.43	***	0.17
Frame interactions: Protection framing x									
Price							-0.0006		0.0009
Condom use							-0.59	*	0.40
Anal sex							-0.13		0.25
Client HIV							0.21	**	0.20
Client STI							0.12		0.23
Opt-out							-0.51		0.22
Respondent characteristic interactions									
Price x married	-0.003	**	0.005	-0.01	***	0.004	-0.003	**	-0.67
Price x low income	0.000		0.001	0.001		0.001	-0.0002		-0.23
Price x experience of IPV in previous 12 months	0.001		0.001	0.002	**	0.001	0.001		1.78
Price x know FSWs who engage in condomless sex	0.001		0.001	0.002	***	0.001	0.001		1.78
Condom x married	1.404	*	1.246	0.87		1.07	1.40	*	1.13
Condom x low income	0.341		0.274	0.13		0.28	0.34		1.24
Condom x experience of IPV in previous 12 months	-0.070		0.292	0.37		0.31	-0.07		-0.24
Condom x know FSWs who engage in condomless sex	-0.010		0.284	-0.55		0.29	-0.01		-0.03

Frame interactions:				
Protection framing x				
Price x married			-0.002	-0.35
Price x low income			0.001	1.21
Price x experience of IPV in previous 12 months			0.001	0.76
Price x know FSWs who engage in condomless sex			0.001	1.35
Condom x married			-0.53	-0.32
Condom x low income			-0.21	-0.54
Condom x experience of IPV in previous 12 months			0.44	1.04
Condom x know FSWs who engage in condomless sex			-0.54	-1.34
Model diagnostics				
Log likelihood	-581.41	-671.39	-1252.79	
AIC	1190.81	1370.78	2561.59	
BIC	1260.70	1440.78	2720.95	
N	122	122	244	

Discussion

This study is the first to consider quantitatively the impact of a hypothetical fully effective HIV prevention product on the economics of sex work. We use stated preference methods to estimate the effect of introducing an effective HIV prevention product on the supply of commercial sex. HIV negative FSW participants completed two identical DCEs at the beginning and end of a larger survey, where the first DCE was framed in the context of current practice (i.e. without alternative HIV prevention protection), and the later DCE framed as if a 100% effective HIV prevention product was readily available and accessible to FSWs. Consistent with prior expectations, we found that this alternate product use increased the influence of price on FSW choices whilst condoms were valued significantly less. Results strongly suggest that alternate product use could reduce the condom differential (price premium for condomless sex) and increase condomless commercial sex. There was some evidence of preference heterogeneity between married and unmarried FSWs, however, our results do not suggest that the response to alternate prevention product introduction will vary much across FSWs. We find that the price of acts does not play an important part in FSW decisions at present, but would be likely to significantly impact choices after the introduction of a fully effective product. This may have implications for future HIV prevention product introduction, although current products have average estimated efficacy which is much lower than condoms[19].

Our simulations of choice data indicate that the condom differential could reduce by up to 73% under use of a fully effective product. Moreover, the quantity of condomless sex provided by FSWs is predicted to more than double with use of a fully protective product. There are three key reasons why this is an important consideration in the HIV prevention response. It is possible that if condom use falls after introducing alternate products, but FSWs are able use these new products effectively, then the projected increase in condomless sex will not substantively affect the HIV epidemic. However,

higher levels of condomless sex could increase the transmission of STIs which are a burden in their own right, but also increase the risk of HIV transmission, thus dampening the overall health benefits of single-purpose products[45]. Theoretical modelling work has shown this may not be important [46], but more research is required.

Some data from oral PrEP trials, largely conducted among MSM populations to-date, indicate that self-reported condom use has not changed among PrEP users[47-50]. Yet, self-reported condom use data could be substantially over-reported, as shown by a list-randomisation study among FSWs in Senegal which estimated that condom use was overestimated by 20 percentage points[51]. In contrast, a number of MSM studies have detected increased STI rates among PrEP users than non-users, an objective indication of increased levels of condomless sex, though it is not generally clear how many detected STIs were pre-existing or newly acquired[52-55]. Mathematical modelling work suggests that, if present, condom substitution may substantively reduce the impact of partially effective products[56, 57]. Future work is required in this area.

This study suggests that effective HIV prevention products could exacerbate the difficulties that FSWs face in negotiating condom use with commercial sexual partners, if clients are aware that FSWs are using highly effective products other than condoms. In this instance, where FSWs are economically vulnerable, or do not have sufficient negotiating power with clients to insist on condom use, alternate product use may increase the occurrence of condomless sex. We also show that FSWs who increase the supply of unprotected sex with PrEP use are simply reacting rationally to exogenous market changes imposed by HIV prevention programmes, and should not face blame or stigma as a result. Instead, any unintended consequences of alternate product introduction should be fully considered by programme implementers through collection of reliable data on act price and condom use, alongside data on coercion from clients to provide condomless sex.

This paper is the first to estimate the effect of new HIV prevention products on the supply of condomless commercial sex. These findings are important for HIV prevention programmes among FSWs as they suggest that condom use may fall after the introduction of new, highly effective HIV prevention products, in part due to the increased importance of act price.

There are strong scientific, economic, and human rights arguments for implementing new HIV prevention products, such as oral PrEP and future alternatives, among FSWs as soon as possible [1], and rollout has begun in many countries including South Africa[21]. The findings of this study do not reduce the public health imperative to make effective HIV prevention products available to FSWs, rather we suggest three things: 1) any unintended consequences of new product implementation should be explicitly measured to assess how the incentive structure of sex work will change as a result of introduction; 2) FSWs who may struggle to adhere consistently to new products should be identified and supported in their adherence, particularly if they are also women who are less able to use condoms consistently; and 3) the impact of new HIV prevention product provision on client attitudes and demands for protected and condomless sex should be monitored, as clients (who already have a strong bargaining position) may place excessive pressure on FSWs perceived to be using alternate protection to provide condomless sex. More research is needed to investigate the extent to which substitution away from condoms occurs following the introduction of different PrEP modalities (i.e. a daily tablet, monthly vaginal ring, six-weekly injection), and to explore how rational economic responses to introduction will affect its impact and cost-effectiveness.

This paper has several limitations. First, the DCE is a simplistic representation of choices in sex work. The description of product use, describing a perfectly effective product with no adherence requirements, does not reflect the imperfect effectiveness of a product such as oral PrEP, and we acknowledge that this may overstate that behavioural

response to HIV protection. In fact, the product profile does not represent the most optimistic scenario of protection from a long-acting injectable. However, this simplistic representation was a pragmatic decision to simplify the choice task itself after extensive piloting showed that participants found it difficult to understand frames describing imperfect effectiveness or additional protection from STIs. It is also unrealistic to assume that FSWs can reliably judge client STI or HIV status. Importantly, the uptake of oral PrEP in demonstration projects and through the health system has been lower than anticipated [58], perhaps because real experience of products provides greater opportunity to make decisions about multiple risks.

Second, the choice task itself assumes that FSWs have a substantial degree of agency over their choice of clients which may not be accurate. However, qualitative research during the design of this study suggests that the large pool of potential clients in this particular setting makes this a reasonable assumption [35], whilst the RDS sample necessarily identified FSWs with some link to peer-educators who are likely to have higher self-efficacy than FSWs not reached by clinical or peer networks. This assumption may not hold for other sex work contexts in South Africa, or beyond.

Third, we use stated preference data on FSW choices because observational revealed preference data from PrEP trials (the newest HIV prevention option to be implemented) or programmes is not yet available. Reassuringly, however, evidence from health focused studies suggests that stated and revealed preferences may be closely correlated [29, 30], whilst even if available, revealed preference data may still be subject to reporting biases.

Fourth, we do not consider the demand side of the commercial sex market, specifically the impact of alternate product use among FSWs on the preferences of clients. If clients know, or perceive FSWs to be using an alternate product such as PrEP, they could use the reduced risk of HIV acquisition in coercive arguments for unprotected sex. Finally,

the diverse nature of sex work within South Africa and across sub-Saharan Africa makes generalisability difficult to assess from this small sample of FSWs.

Conclusion

We explored how the introduction of effective HIV prevention products might influence the economics and supply of condomless commercial sex. By applying stated preference methods in the form of a repeated discrete choice experiment, we show that introducing an 100% effective HIV prevention product may double the number of condomless acts supplied, and considerably reduce (by 73%) the price premium for condomless sex through decreasing the value placed on condoms and increasing the utility obtained from act price. These findings have implications for the possible impact of new HIV prevention product rollout, among FSW groups, which is proceeding worldwide, especially in scenarios where women may find adherence to tablet based prevention difficult. In these settings, the reduced use of condoms may reduce the impact of an alternate HIV prevention product. Further research is needed on the revealed preferences of FSWs and clients to assess how new products such as PrEP and associated economic incentives related to condomless sex affect health choices in commercial sex to allow appropriate support interventions to be put in place.

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Supplementary Appendix I: Willingness to accept ratios

	WTA: No framing MNL			WTA: PrEP framed MMNL		
	Coeff.	SE		Coeff.	SE	
Price	1	-	-	1	-	-
Condom use						
Condom*PrEP framing	11721.8	10436.5		3184.3	***	804.9
Type of sex						
Anal*PrEP framing	-7529.0	6907.2		-2572.1	***	709.4
Perceived client HIV risk						
Think client has HIV*PrEP framing	-1240.4	1117.4		-207.3	**	87.2
Perceived client STI risk						
Think client has STI*PrEP framing	-2156.5	2150.7		-549.3	***	174.1
Opt-out (no services to either)						
Opt-out*PrEP framing	3795.5	3135.1		860.6	***	227.1

Conclusions from paper R3

Paper R3 is the first to estimate the impact of new HIV prevention products on the supply of condomless commercial sex. It provides evidence that introducing effective HIV prevention products may cause a change in condom use and pricing behaviours among FSWs, potentially leading to an increase in the supply of condomless commercial sex. It is possible that introducing effective new products might exacerbate pressures on FSWs to provide condomless sex. Since oral PrEP, as currently provided in South Africa, does not protect against other STIs or unwanted pregnancy, increases in condomless sex may lead to increases in these. Furthermore, if HIV prevention products cannot be used effectively by FSWs, or if they stimulate a change in risky behaviours as a result of changing economics, such as leading to an increase in the provision of commercial acts, the impact of PrEP may be substantially reduced.

Chapter 9: Paper R4 – How could risk compensation change the impact of new HIV prevention products? Modelling stated preference evidence from female sex workers

Overview of paper R4

Paper R3 provides evidence that introducing effective HIV prevention products may lead to a decrease in the price premium for unprotected sex, and a potential increase in the supply of condomless sex. This paper, R4, uses simulations from this DCE to parameterise scenarios in a dynamic transmission model. In addition, it incorporates economic theory to describe how labour supply can be impacted by changing financial incentives for work. This paper meets objective 4 to explore if changing incentives in sex work could substantially impact the impact of HIV prevention products through risk compensation.

This paper has been prepared for submission to Health Economics, and is awaiting co-author comments ahead of submission.



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RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

Student	Matthew Quaife
Principal Supervisor	Fern Terris-Prestholt
Thesis Title	Using stated preferences to estimate the impact of new HIV prevention products in South Africa

If the Research Paper has previously been published please complete Section B. If not please move to Section C

SECTION B – Paper already published

Where was the work published?	
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If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Health Economics
Please list the paper's authors in the intended authorship order:	MQ, ZM, PV, FTP
Stage of publication	Pre-submission draft

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	lead + carried out analysis, wrote first draft + revised w/ co-author comments.
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Student Signature: _____

Date: 17/7/17

Supervisor Signature: _____

Date: 17/7/17

How could risk compensation change the impact of new HIV prevention products?

Modelling stated preference evidence among female sex workers

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Author Contributions: Conceived the study: MQ, FTP, PV, constructed the model: MQ ZM, wrote first draft: MQ, interpreted results, contributed to and approved final manuscript: MQ, ZM, FTP, PV.

Abstract

Female sex workers (FSWs) face substantial health risks, not least through exposure to HIV and other sexually transmitted infections (STIs). Many groups face these, however FSW choices are complicated by the existence of financial incentives to provide riskier services to clients, such as unprotected sex, for an increased price. The development and early roll-out of efficacious pre-exposure prophylaxis (PrEP) for HIV prevention offers promise in enabling FSWs to protect themselves from HIV without relying on clients to use a condom. Yet a lower risk associated with providing unprotected sex, coupled with financial incentives to do so, may lead to risk compensation: a reduction in condom use, an increase in the amount of sex supplied, or both. This paper integrates economic theory into a dynamic transmission model to explore how risk compensation might change the impact of PrEP. Scenarios modelling changes in condom use and the quantity of unprotected sex supplied were parameterised by combining simulations from stated preference data with microeconomic theory. Competition between PrEP users and non-users was also considered. Results indicate that the impact of PrEP could be highly sensitive to risk compensatory behaviours, including those driven by changes in the economics of sex work. In addition, the extent to which competition affects the behaviours of non-PrEP users is also important to results. We find that current transmission models, which do not commonly consider risk compensation, may overestimate the impact of HIV prevention products. Further research is needed to explore potential risk compensatory behaviours among FSWs and clients, and data is required to assess the impact of non-user behaviour.

Introduction

Women engaged in commercial sex, or female sex workers (FSWs), face daily health risks, not least from sexually transmitted infections (STIs) including the human immunodeficiency virus (HIV)[1]. In some areas of sub-Saharan Africa, the HIV prevalence among FSWs is estimated to be at least 50%[2] and as a result FSWs and their clients are termed *key populations* in the HIV response[1]. Like other key populations enhanced HIV testing, treatment, and prevention programmes are frequently focused on FSW and client populations[1].

FSWs face different choices and incentives from other key populations. In addition to navigating the complexities of non-commercial sexual relationships, the economic context of sex work means that FSWs can face strong price competition from other commercial sex providers, alongside client resistance to condom use, including threats and use of violence[3-6]. In many circumstances FSWs are financially dependent on sex work to support themselves and their families[7].

A large body of economic research on sex work has shown that financial incentives are positively correlated with the HIV, STI, and pregnancy risk borne by FSWs. In all published econometric studies to-date, a compensating differential, or price premium, has been shown to exist for unprotected sex compared to protected sex. Anecdotal evidence of this differential (e.g. [6]) was first empirically estimated by Rao et al.[8] who found a price premium of 79% for unprotected sex among Indian FSWs, terming this the *condom differential*. Further econometric evidence has estimated a price premium between 7% (Belgium and the Netherlands) and 81% (Bangladesh)[8-14]. In addition, evidence has shown that the size of the price premium depends on workplace conditions, and the bargaining power of FSWs[15]. Similar patterns have been seen in data from male sex workers, although risks and market factors differ substantively from those facing FSWs[16].

Recent technological developments have led to the development of antiretroviral-based HIV prevention products, for use as pre-exposure prophylaxis (PrEP)[17]. When used effectively, PrEP products, which currently exist in oral tablet, topical gel and intravaginal ring form, have been shown to offer very high levels of HIV protection[18]. Yet PrEP effectiveness – a function of product efficacy and adherence – has been shown to vary across different population groups and in different contexts, whilst products to-date only offer protection from HIV, and not STIs or pregnancy (ibid.). As such, condoms remain a critical part of the HIV prevention armoury, and PrEP users are encouraged to use condoms consistently alongside ARV-based products[19].

In a standard consumer demand model, agents respond to technologies that reduce the risk of a utility-providing behaviour by increasing consumption of this behaviour. In other words, if PrEP reduces the risk associated with unprotected sex, then FSWs may increase the quantity of unprotected sex that they supply. This response, termed risk compensation, means that the anticipated impact of PrEP may be smaller than predicted [20]. In recent years, developments in the science of HIV prevention have been met with concerns that risk compensation may mitigate the impact of interventions on the epidemic (e.g. [21, 22]). If individuals overestimate the benefits of interventions, or if there are externalities associated with the behaviour, risk compensatory behaviours may even lead to interventions having a negative overall impact on welfare. This paper explores this hypothesis.

This paper makes three contributions to the economic and epidemiological literatures on risk compensation in HIV prevention. Firstly, this is the first study to explicitly integrate economic behaviour into a HIV transmission model. Specifically, we set the amount of condom-protected and unprotected sex supplied to be dependent on economic considerations of act-price and the behavioural economic concept of income targeting[23], obtained from stated preference data. Secondly, we explicitly model

competition between prep-using and non-using FSWs to account for the externalities associated with risk compensation in a competitive market. We assume that demand for unprotected sex among clients is persistent, and the PrEP-using section of the market is willing to provide this at a lower price. Thus, to remain competitive, non-users must adjust their willingness to accept risk. Thirdly, this is the first study to explicitly model risk compensation among FSWs based on empirical (stated preference) data.

There has been no published evidence to-date from FSW populations that condom use is markedly reduced under PrEP use (e.g. [24]). Yet condom use data are largely self-reported and subject to acceptability biases [25, 26]. Studies among other groups of PrEP users have detected increased STI rates among PrEP users than non-users, an objective indication of increased levels of condomless sex [27-30].

This study uses stated preference data to parameterise a mathematical dynamic transmission model of HIV infection among FSWs and clients. Mathematical models are widely used to estimate the potential impact and cost-effectiveness of HIV treatment and prevention interventions among FSWs, including PrEP (e.g. [31-35]). To-date, only a handful of models explicitly account for condom substitution or other forms of risk compensation. When modelled, the existence and magnitude of condom substitution due to PrEP has not been driven by data or a strong theoretical justification. Foss et al.[36] and Grant et al.[37] predict that condom substitution could only be tolerated among FSWs with lower levels of condom use, or if the effectiveness of PrEP was higher than currently estimated (>75%). Mitchell et al.[38] found that a 50% reduction in condom use by PrEP users would negate the beneficial impact of PrEP. Among MSM in the UK, Punyacharoensin et al.[39] estimated that PrEP effectiveness would be significantly reduced if the amount of condomless sex or number of sexual partners increased by 50%.

In a previous study, we used a hypothetical discrete choice experiment (DCE) to show that PrEP is likely to substantively impact the economics of sex work[40]⁹. DCEs are commonly applied in health to elicit preferences for products or services before they are introduced[41], and have been shown to have reasonable predictive accuracy[42]¹⁰. Specifically, we found that condoms became less influential and price became more influential under PrEP use. Behavioural simulations from the DCE suggest that the condom differential, the price of unprotected sex relative to that of protected sex, would fall by 73% from ZAR 411 to ZAR 172 whilst the amount of unprotected sex supplied could more than double, increasing by a factor of 2.3.

Although interesting, these findings do not immediately tell us how the impact of PrEP could be affected by changes to the economics of sex work. Therefore, in this paper we combine these results with theory from classical and behavioural microeconomics to explore how the PrEP impact might be affected by changes in the economics of commercial sex. We parameterise a compartmental dynamic transmission model to represent a generic sub-Saharan African HIV epidemic among FSWs and their clients. To get an understanding of how the impact of PrEP use could be affected by economic effects, we take a stepwise approach including five scenarios, with each scenario incorporating additional complexity.

Methods

We parameterised a deterministic, compartmental dynamic model of HIV transmission among FSWs and male clients to match the characteristics of a generic, large sub-Saharan Africa HIV epidemic.

In the following five scenarios, we introduce additional complexity from economic theory at each stage:

⁹ Chapter 11 of this thesis

¹⁰ Chapter 5 of this thesis

Scenario 1 makes the same assumption as many mathematical models, of no condom substitution due to PrEP use.

Scenario 2 uses simulations from the DCE to predict the degree of condom substitution that would occur amongst PrEP users, holding all other sexual behaviours and condom use in non-PrEP users constant.

Scenario 3. Since the DCE predicts that PrEP users will accept a (73%) lower price to provide unprotected sex compared to non-users, this scenario uses a theory from microeconomics – the target income hypothesis – to hypothesise that FSWs on PrEP will increase their frequency of commercial sex to compensate for this reduction in income to ensure a the same income.

Scenarios 4 and 5 take a whole-market perspective to acknowledge that the behaviour of PrEP non-users may be affected by that of PrEP users, depending on the extent of PrEP coverage, due to competition in supply to a limited client base. To our knowledge this is the first mathematical model of infectious disease to explicitly incorporate behavioural patterns from economic theory.

Building economics into a transmission model

This section demonstrates how we allow economic factors to influence the behaviours which are important to an infectious disease model. In the simplest economic model, income is defined as the price of a good multiplied by the quantity supplied. Here we assume that FSWs only provide commercial sex acts, which can be a) condom-protected (denoted by the subscript c), or b) condom-less or unprotected (denoted by the subscript nc). Thus:

$$M_j^k = Q_{cj}^k * P_{cj}^k + Q_{ncj}^k * P_{ncj}^k \quad (1)$$

Where M represents the total income from sex work, Q_{nc}^k and Q_c^k are the number of condomless and protected sex acts supplied, respectively, and P_{nc}^k and P_c^k are the price paid for condomless and protected sex acts, respectively. We divide FSWs into categories $k = \{prep, noprep\}$ for each scenario $j = (1,2,3,4,5)$, where $j=1$ refers to the baseline scenario where PrEP has not been introduced.

As discussed, the economic literature has explored the dynamics of P_c^k and P_{nc}^k , specifically the distance between prices (the condom differential) and changes associated with the health risks associated with each type of act. However, the important parameters for an HIV transmission model are not the price but the quantity and type of sex acts in the market.

If we assume the level of condom use for PrEP users and non-users (k) is π_j^k for each scenario (of how PrEP use effects condom use ($j=1,..,5$)), then the number of protected and condomless sex acts can be defined as follows:

$$Q_{cj}^k = N_j^k(\pi_j^k) \quad (2)$$

$$Q_{ncj}^k = N_j^k(1 - \pi_j^k) \quad (3)$$

Where N_j^k is the number of sex acts for PrEP users and non-users in each scenario.

Substituting (2) and (3) into (1) and factorising:

$$M_j^k = N_j^k(\pi_j^k \times P_{cj}^k + (1 - \pi_j^k) \times P_{ncj}^k) \quad (4)$$

The DCE results allow us to predict the relative change in the frequency of condomless sex compared to condom-protected sex for FSWs that start using PrEP, ρ_j^{prep} and ρ_j^{noprep} . We use the parameter ρ_j^k to adjust how baseline condom use, π_1^k , is affected in each scenario.

$$\pi_j^k = 1 - (1 - \pi_1^k)\rho_j^k \quad (5)$$

Predicting risk compensation from stated preference data

The DCE study [40]¹¹ estimated that use of an effective HIV prevention product would reduce the amount of money a FSW would need to compensate for the disutility of providing unprotected sex to a client. We use predicted probability analysis to simulate the impact of a fully effective prevention product on the price and supply of protected and condomless sex. As elsewhere in the health literature [43-45], we predict the supply response to product introduction by summing the model coefficients with imputed attribute levels. As best-practice in predicting with stated preference data, we rescale results for simulation using revealed preference data. We hold the price of protected sex constant (ZAR 72, USD \$5.41) take the absolute price premium as self-reported by FSWs (ZAR 394, USD \$29.50), and reduce it by 73% to generate the new price of condomless sex (ZAR 106, \$8).

Description of transmission model

The model structure is relatively simple, and divides HIV negative FSWs by PrEP status, and HIV positive clients and FSWs by acute, chronic, and AIDS state infections alongside engagement with antiretroviral treatment (ART). In addition to cessation of FSW or client status, individuals leave the population due to natural mortality from all compartments, or AIDS-related mortality from AIDS compartments. ART users are assumed to progress through the same acute-chronic-AIDS stages of HIV infection as non-users, but at a slower rate. ART dropout is modelled, with reinitiation assumed to be the same rate as ART-naïve individuals. ART initiation is assumed to occur in chronic and AIDS stages, but not at acute infection.

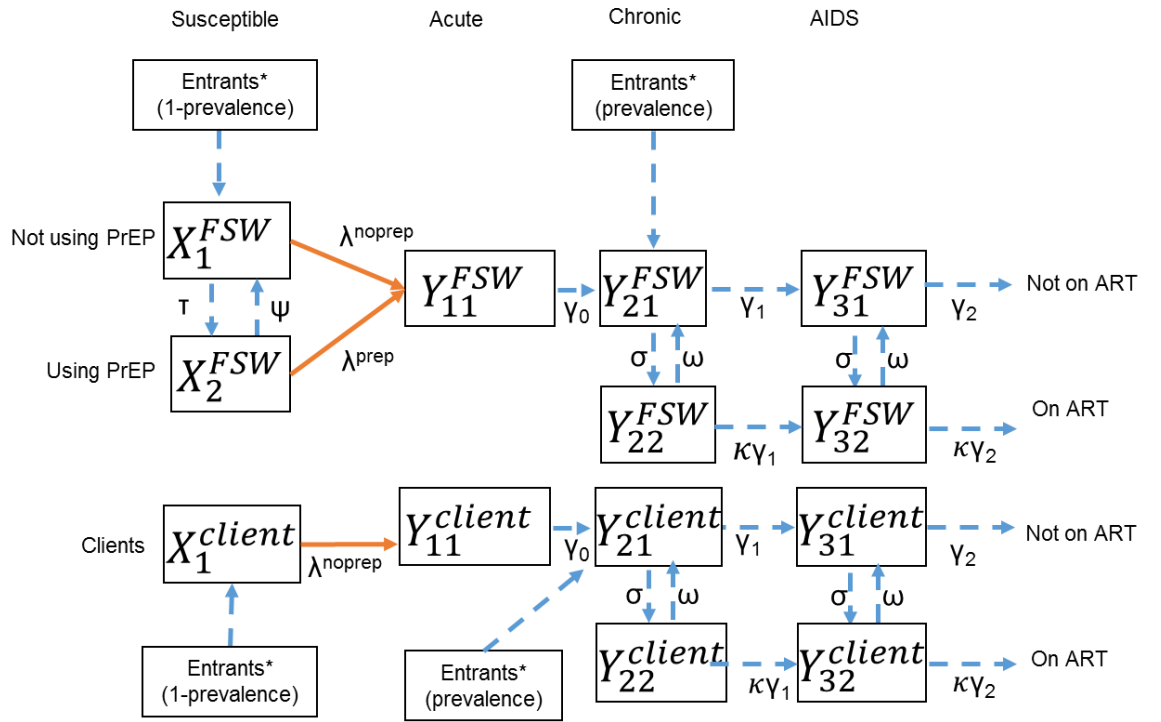
¹¹ Chapter 11 of this thesis

Individuals enter the model in the HIV negative or chronic compartments according to estimates of HIV prevalence in the general population. The infectivity of HIV positive persons is assumed higher in acute and AIDS stages relative to chronic infection. Infectivity is reduced for persons using ART.

The transmission model

Figure 1 shows the model structure, and the generalised model as a system of differential equations is shown below.

Figure 1: Model structure



Female sex workers

$$\frac{dX_{1,i}^{FSW}}{dt} = (1 - prevalence_i^{FSW})T_i^{FSW}(\zeta_i^{FSW} + \mu) + X_{2,i}^{FSW}\psi_i - X_{1,i}^{FSW}\lambda_i^{noprep} - X_{1,i}^{FSW}(\tau_i + \zeta_i^{FSW} + \mu)$$

$$\frac{dX_{2,i}^{FSW}}{dt} = X_{1,i}^{FSW}\tau_i - X_{2,i}^{FSW}\lambda_i^{prep} - X_{2,i}^{FSW}(\psi_i + \zeta_i^{FSW} + \mu)$$

$$\frac{dY_{11,i}^{FSW}}{dt} = X_{1,i}^{FSW} \lambda_i^{noprep} + X_{2,i}^{FSW} \lambda_i^{prep} - Y_{11,i}^{FSW} (\gamma_{0,i} + \zeta_i^{FSW} + \mu)$$

$$\begin{aligned} \frac{dY_{21,i}^{FSW}}{dt} = & prevalence_i^{FSW} T_i^{FSW} (\zeta_i^{FSW} + \mu) + Y_{11,i}^{FSW} \gamma_{0,i} + Y_{22,i}^{FSW} \omega_i \\ & - Y_{21,i}^{FSW} (\gamma_{1,i} + \sigma_i + \zeta_i^{FSW} + \mu) \end{aligned}$$

$$\frac{dY_{31,i}^{FSW}}{dt} = Y_{21,i}^{FSW} \gamma_{1,i} + Y_{32,i}^{FSW} \omega_i - Y_{31,i}^{FSW} (\gamma_{2,i} + \sigma_i + \zeta_i^{FSW} + \mu)$$

$$\frac{dY_{22,i}^{FSW}}{dt} = Y_{21,i}^{FSW} \sigma_i - Y_{22,i}^{FSW} (\kappa \gamma_{1,i} + \omega_i + \zeta_i^{FSW} + \mu)$$

$$\frac{dY_{32,i}^{FSW}}{dt} = Y_{22,i}^{FSW} \kappa \gamma_{1,i} + Y_{31,i}^{FSW} \sigma_i - Y_{32,i}^{FSW} (\kappa \gamma_{2,i} + \omega_i + \zeta_i^{FSW} + \mu)$$

Clients

$$\begin{aligned} \frac{dX_{1,i}^{client}}{dt} = & (1 - prevalence_i^{client}) T_i^{client} (\zeta_i^{client} + \mu) - X_{1,i}^{client} \lambda_i^{noprep} - X_{1,i}^{client} (\zeta_i^{client} \\ & + \mu) \end{aligned}$$

$$\frac{dY_{11,i}^{client}}{dt} = X_{1,i}^{client} \lambda_i^{noprep} - Y_{11,i}^{client} (\gamma_{0,i} + \zeta_i^{client} + \mu)$$

$$\begin{aligned} \frac{dY_{21,i}^{client}}{dt} = & prevalence_i^{FSW} T_i^{client} (\zeta_i^{client} + \mu) + Y_{11,i}^{client} \gamma_{0,i} + Y_{22,i}^{client} \omega_i - Y_{21,i}^{client} (\sigma_i \\ & + \gamma_{1,i} + \zeta_i^{client} + \mu) \end{aligned}$$

$$\frac{dY_{31,i}^{client}}{dt} = Y_{21,i}^{client} \gamma_{1,i} + Y_{32,i}^{client} \omega_i - Y_{31,i}^{client} (\gamma_{2,i} + \sigma_i + \zeta_i^{client} + \mu)$$

$$\frac{dY_{22,i}^{client}}{dt} = Y_{21,i}^{client} \sigma_i - Y_{22,i}^{client} (\kappa \gamma_{1,i} + \omega_i + \zeta_i^{client} + \mu)$$

$$\frac{dY_{32,i}^{client}}{dt} = Y_{22,i}^{client} \kappa \gamma_{1,i} + Y_{31,i}^{client} \sigma_i - Y_{32,i}^{client} (\kappa \gamma_{2,i} + \omega_i + \zeta_i^{client} + \mu)$$

We define θ as the overall effectiveness of PrEP incorporating those that use PrEP adherently or not, β_{mf} the per act transmission probability from a HIV positive male to a

HIV negative female and vice versa for β_{fm} , and ε the efficacy of condoms. The force of infection for FSWs using and not using PrEP in scenario j are presented below, where T^{client} and T^{FSW} represent the total number of clients and FSWs, η_{acute} , and η_{AIDS} represent heightened transmissibility of HIV positive persons in acute and AIDS stages respectively, and η_{ART} reduced transmissibility attributable to ART use:

$$\lambda_{FSW}^{prep} = \beta_{mf} * \left[N_{FSW,j}^{prep} * \left(\frac{\eta_{acute} Y_{11}^{client} + Y_{21}^{client} + \eta_{AIDS} Y_{31}^{client} + \eta_{ART} (Y_{22}^{client} + Y_{32}^{client})}{T^{client}} \right) \right] * [(1 - \varepsilon \pi_j^{prep}) * (1 - \theta)]$$

$$\lambda_{FSW}^{noprep} = \beta_{mf} * \left[N_{FSW,j}^{noprep} * \left(\frac{\eta_{acute} Y_{11}^{client} + Y_{21}^{client} + \eta_{AIDS} Y_{31}^{client} + \eta_{ART} (Y_{22}^{client} + Y_{32}^{client})}{T^{client}} \right) \right] * (1 - \varepsilon \pi_j^{noprep})$$

$$\lambda_{CLIENT}^{noprep} = \beta_{fm} * \left[N_{CLIENT,j}^{noprep} * \left(\frac{\eta_{acute} Y_{11}^{FSW} + Y_{21}^{FSW} + \eta_{AIDS} Y_{31}^{FSW} + \eta_{ART} (Y_{22}^{FSW} + Y_{32}^{FSW})}{T^{FSW}} \right) \right] * (1 - \varepsilon \pi_j^{noprep})$$

Model parameterisation

The size of the FSW population was assumed to be 132,000 as estimated for South Africa in 2013[46] and the client population ten times this based on a population balance equation. FSWs cease sex work at a rate of 14% per year (ζ^{FSW}) which assumes the average length of time in sex work as seven years, the third quartile of self-reported time in sex work in a 2015 cross-sectional survey of FSWs in South Africa[47]. We assume that clients cease sex work at a rate of 10% per year (ζ^{client}), implying that individuals

are clients for, on average, ten years. The rate of entry to being a FSW or client was assumed equal to the exit rate of both before accounting for HIV-related death.

Self-reported estimates of condom use can be higher than reality due to acceptability bias[26]. The DCE survey in South Africa asked a number of questions which aimed to estimate condom use, as described in supplementary Table S1. We use the middle value of these to parameterise condom use, the proportion of FSWs who reported charging any price for unprotected acts, at 78%. For the simplest PrEP scenario modelled, we assume this remains unchanged among both PrEP users and non-PrEP users i.e. there is no condom substitution. In later scenarios, we model the impact of condom substitution.

Parameters for the baseline number of sex acts provided by FSWs per month (33) were also taken from the primary survey in South Africa[40]; this parameter was found to be within the interquartile range of other FSW surveys in South Africa[48].

Biological parameters and the efficacy of condoms and ART in preventing HIV transmission were obtained from published literature. The multiplicative factors by which the probability of HIV transmission during the AIDS and acute HIV phases are increased compared to the chronic stage are taken from meta-analysis data[49]. The effectiveness of ART in reducing progression to the AIDS state and death is assumed to be 92%, taken from published studies[50, 51]. Details of model parameters are included in Table 1.

Table 1: Summary of model parameters

Parameter	Symbol	Value	Lower	Upper	Source
FSW population size	T_{FSW}	132000	131000	182000	[46]
Client population size	T_{client}				
PrEP uptake rate	τ	15%	5%	30%	[47]
PrEP dropout rate	ψ	20%			Assumption as in [38]
Condom efficacy	ε	80%	66%	94%	[52]
Treatment initiation rate	σ	0.3654	0.3132	0.4698	58% [47], 63% linking per year [53]
ART failure rate	ω	0.04	0.01	0.07	[54]
Multiplicative factor modelling the reduced progression to AIDS due to ART treatment	χ	0.3			Assumption as in [38]
Natural death rate (FSWs and clients)	μ	0.02			1/ life expectancy of 62.4 [55]
Exit rate from sex work	ζ_{FSW}	0.1333333			Upper IQR [47]
Exit rate from being a client	ζ_{client}	0.098	0.091	0.105	Assumption as in [38]
1/Duration of acute HIV stage	γ_1	0.242	0.103	0.381	[56]
1/Duration of chronic stage	$1/\gamma_2$	10.05	9.28	10.81	[56]
1/Duration of AIDS stage	$1/\kappa$	0.83	0.61	1.06	[56]
Multiplicative transmission factor in the acute stage	η_{acute}	11.65	4.5	18.8	[49]
Multiplicative transmission factor in the AIDS stage	η_{AIDS}	8.15	4.4	11.9	[49]
Multiplicative transmission factor due to treatment	η_t	0.08	0	0.16	[50, 51]
Female to male per act transmission probability	β_{fm}	0.0004			[57]
Male to female per act transmission probability	β_{mf}				[57]
Baseline condom use	π	78%			As described, taken from [47]
Starting FSW Prevalence		18%			Assumption
Starting client prevalence		9.9%	8.90%	11%	South Africa [58]

Gen pop male prevalence	9.90%	8.90%	11%	South Africa [58]
Gen pop female prevalence	14.40%	13.30%	15.60%	South Africa [58]
PrEP adherence	50/75%	0.5	0.75	Assumption
Monthly clients seen by FSW	33	27	45	[47]
Price of protected act	83			[47]
Price of unprotected act	811			[47]

Model calibration

We do not fit the model to a particular epidemic, but use general HIV prevalence and treatment coverage assumptions based on published data, including that from South Africa. A baseline HIV prevalence of 18% is seeded into the epidemic in 2004, 13 years before the assumed introduction of PrEP, and is in line with empirical estimates of FSW prevalence in the general population in South Africa [34]. The transmission parameter for male to female transmission (β_{mf}) was reduced from a starting value of 0.008, as estimated by the US Centers for Disease Control[57], to 0.006 to give results in a stable HIV prevalence of 19% in 2017 when PrEP interventions are introduced. The female to male transmission parameters (β_{fm}) was assumed to be 0.004 (ibid.). Treatment coverage is broadly matched to observed scale-up from zero coverage in 2004 to around 70% coverage in 2017.

Impact analyses

To make estimates of absolute changes to PrEP effectiveness conservative, PrEP efficacy was assumed to be 71%, the highest estimated among female groups in a PrEP trial to-date[59], and we assume high and low adherence scenarios of 75% and 50%. PrEP impact is quantified as the absolute change in HIV infections compared to a counterfactual scenario of no rollout. Table 2 shows how economic parameters vary across scenarios.

Base case PrEP use, no condom substitution

The scenario 1 is the current approach used in many PrEP impact models, and does not account for potential economic influences on behaviour. As per the authors' previous work predicting demand for PrEP among this group of FSW respondents, we estimate PrEP uptake to be 15%[60]¹².

¹² Chapter 10 of this thesis

Condom substitution response among PrEP users

The DCE [40]¹³ predicted that under PrEP use, the price premium for condomless sex will fall by 73% (from ZAR 411 to ZAR 172 per condomless sex act) and the quantity of condomless sex will increase 2.3-fold, i.e. $\rho_{jk} = 2.3$. Substituting this into equation (5) suggests that, among PrEP users, the consistency of condom use π_1^{prep} decreases from 78% to 50% of sex acts, i.e. non-condom protected sex acts in PrEP users increases from 22% to $22\% \times 2.3 = 50.6\%$

In this scenario, we assume that PrEP use only affects the condom use of FSWs using PrEP, and hold the level of condom use for non-PrEP users constant (i.e. assuming that there is no competition between these FSWs). We also assume no change in the total number of sex acts provided, and that PrEP use has no effect on the price charged for sex with a condom. This means that FSWs using PrEP will bear an 18% income reduction of ZAR 920 (USD \$71) per week, whereas FSWs not using PrEP will see no reduction in income.

Constant income hypothesis: adjusting quantity supplied

This scenario extends scenario 2 by incorporating evidence from behavioural microeconomics, the target income hypothesis. Economic research has shown that, in contrast to the predictions of classical model, when suppliers are faced with an exogenous shock to wages, they adjust the quantity supplied to keep income constant within a particular period of time. The target income hypothesis, popularised in the seminal study by Camerer et al. [23], demonstrated that taxi drivers in New York City make supply decisions with a reference-dependent income target, cease working when it is reached – working less hours when wages are higher. Similar results, indicative of a backward-bending supply curve, have been found in studies among Singaporean taxi drivers [61] baseball stadium vendors [62], and Swiss bicycle messengers [63].

¹³ Chapter 11 of this thesis

Following from this literature, in scenario 3 we assume that FSWs also respond to price shocks through pursuing an income target. As in scenario 2, we assume that the price of condomless sex falls by 73% under PrEP use, and the price of sex with a condom remains constant at P_{nc1}^{prep} . However, we assume that PrEP users increase their overall frequency of commercial sex to ensure the same income. We therefore want to find the new frequency of sex N_3^{prep} which gives the same income, which we obtain through rearranging equation (4):

$$N_3^{prep} = \frac{M_0^{prep}}{P_{c0}\pi_3^{prep} + (1 - \pi_3^{prep})\alpha_j P_{nc0}^{prep}} \quad (6)$$

Where the ratio of prices for condomless sex with and without PrEP $\alpha_j = 2.3$, obtained from the DCE. We assume that the consistency of condom use among PrEP users π_3^{prep} is 50% of acts, as in scenario 2, but set the weekly income as fixed to the same level as before the introduction of PrEP (M_0^{prep} =ZAR 5120 or USD \$400). As before, we assume that the FSWs using PrEP have no impact on the level of condom use of non-PrEP users and does not affect the price they can charge for condomless sex. We consider the impact of this scenario for different PrEP coverage levels amongst FSW.

A competitive market: Non-PrEP users change the amount of sex supplied

The previous scenarios assume that only PrEP users respond to changing market conditions caused by the introduction of PrEP. A more realistic assumption would be that the dynamics of the commercial sex market would shift to some extent for all FSWs, not just those using PrEP, due to working in a competitive market. For example, non-PrEP users would also face pressures to charge lower prices for condomless sex and/or increase their supply of condomless sex.

We model the potential impact of this competition in scenarios 4 and 5. Scenario 4 assumes that non-PrEP users face pressure to reduce the price of condomless sex due to the reduction in price by PrEP users. However, we assume that this will be related to the

uptake of PrEP; when PrEP uptake is low, non-PrEP users will only see a small effect of competition, whereas if PrEP use is higher, then non-users are more likely to feel the effect of competition.

We account for this by using a parameter to mediate the extent to which the behaviour of non-PrEP users tends to that of PrEP users. This factor $H_j^{noprep} = \Omega_j U_j$ describes the extent by which overall PrEP uptake U_j affects the behaviour of non-PrEP users according to a *competition coefficient*, Ω_j bounded [0,1], which determines the extent to which uptake impacts behaviour. For example, if PrEP uptake is 20% and Ω_j set to 1, then the price of condomless sex among non-PrEP users would be 20% closer to what it is among PrEP users compared to before PrEP. If Ω_j is reduced to 0.5, then the impact of competition would be halved. In the base case, Ω_j is set to 0.5 with variation explored in a sensitivity analysis.

In scenario 4 we assume that non-PrEP users *will not* start providing more condomless sex, and hold condom use constant (i.e. set $\rho_j^{noprep} = 1$, though maintain $\rho_j^{prep} = 2.26$). Instead, we assume that non-PrEP users will increase their total number of commercial sex acts to maintain their current income, while assuming a lower price for unprotected sex.

To calculate the new price of unprotected sex among non-PrEP users, we relate the price of condomless sex among non-PrEP users to that of PrEP users using price values obtained from DCE simulation and factor H_j (here listed as calculated in scenario 1):

$$P_{nc4}^{noprep} = P_{nc1}^{noprep} - H_j(P_{nc1}^{noprep} - P_{nc1}^{prep}) \quad (7)$$

This value is substituted into equation (6) to calculate the number of acts provided by non-PrEP users.

A competitive market: Non-PrEP users change the amount and type of sex supplied

In extension to scenario 4, instead of competition only inducing an increase in the *number* of acts among non-PrEP users, we assume that non-PrEP users change both the *number* (N_{jk}^{noprep}) and the *type* (π_{jk}^{noprep}) of sex acts supplied according to the behaviours of PrEP users, i.e. they also increase their rate of unprotected sex acts based on the same competition coefficient that we hypothesised would affect the price of unprotected sex. Extending (5) we see that:

$$\pi_j^{noprep} = \pi_1^{noprep} - H(\pi_1^{noprep} - \pi_j^{prep}) \quad (8)$$

We then substitute π_j^{noprep} from equation (8) into equation (6).

Table 2: Variation in economic parameters

	Counterfactual		Scenario 1 Base case, no condom substitution		Scenario 2 Condom substitution among PrEP users		Scenario 3 Constant income hypothesis – PrEP users increase the quantity supplied		Scenario 4 Competition – Non-PrEP users increase the amount of sex supplied		Scenario 5 Competition – Non-PrEP users change the amount and type of sex supplied	
	PrEP users	non-PrEP users	PrEP users	non-PrEP users	PrEP users	non-PrEP users	PrEP users	non-PrEP users	PrEP users	non-PrEP users	PrEP users	non-PrEP users
Condom use	N/A	78%	78%	78%	50%	78%	50%	78%	50%	78%*	50%	50-78%*
Number of commercial sex acts per month	N/A	33	33	33	33	33	40	33	40	33	40	33-40*
Price of unprotected act	N/A	411	411	411	172	411	172	411	172	172-411*	172	172-411*
Price of protected act	N/A	83	83	83	83	83	83	83	83	83	83	83
Monthly income from sex work (ZAR)	N/A	5,120	5,120	5,120	4,199	5,120	5,120	5,120	5,120	5,120	5,120	5,120

*Dependent on $H=\Omega \cdot \text{PrEP coverage}$. Parameters in bold signify marginal changes in each scenario as compared to the previous. ZAR 5120 = USD \$385.26, ZAR 4199 = USD \$316.

Results

Baseline prevalence and incidence trends

Without a PrEP intervention and as shown in Figure 2, the model predicted a stable HIV epidemic for the period modelled between 2004 and 2037 with HIV prevalence in FSW predicted to be between 22 and 25% after being seeded at 25% initially. Client prevalence was seeded at 30% and increased, at a decreasing rate, to around 60% towards the end of the modelled period.

Figure 2 shows projection of HIV prevalence under the scenarios modelled, with the baseline (no intervention) projection shown by the black line. Because we only model a low coverage of PrEP in this scenario, the impact achieved is not large for any scenario.

Scenario 1: Base case, no condom substitution

Scenario 1 (red line in Figure 2), where condom use is assumed to remain constant under PrEP use, shows the greatest reduction in HIV prevalence of all of those modelled. For the low adherence (50%) scenario, we project a 3.7% reduction in total HIV infections over the 20 years following the introduction of PrEP, corresponding to a 0.4 percentage point decrease in overall HIV prevalence. Conversely, for the high adherence (75%) scenario, we predicted an 5.7% reduction in total infections and a 0.6 percentage point decrease in HIV prevalence.

Scenario 2: Condom substitution among PrEP users

Scenario 2 (blue line in Figure 2) assumes that PrEP users engage in risk compensation and so increase the proportion of unprotected sex acts after PrEP initiation. Under the assumption of low (50%) adherence, the model suggests that risk compensation due to PrEP would stimulate sufficient risk compensation to negate its impact, resulting in a 0.1% increase in total HIV infections over the 20 years after the introduction of PrEP. For the high adherence scenario (75%), the reduction in impact is less, with the decrease

in HIV infections reducing to 5.7% over 20 years and HIV prevalence reducing by 0.3 percentage points.

Figure 2: Impact of low or high adherence PrEP use on HIV prevalence among FSWs for different scenarios of how PrEP use affects frequency of, and condom use in, commercial sex acts

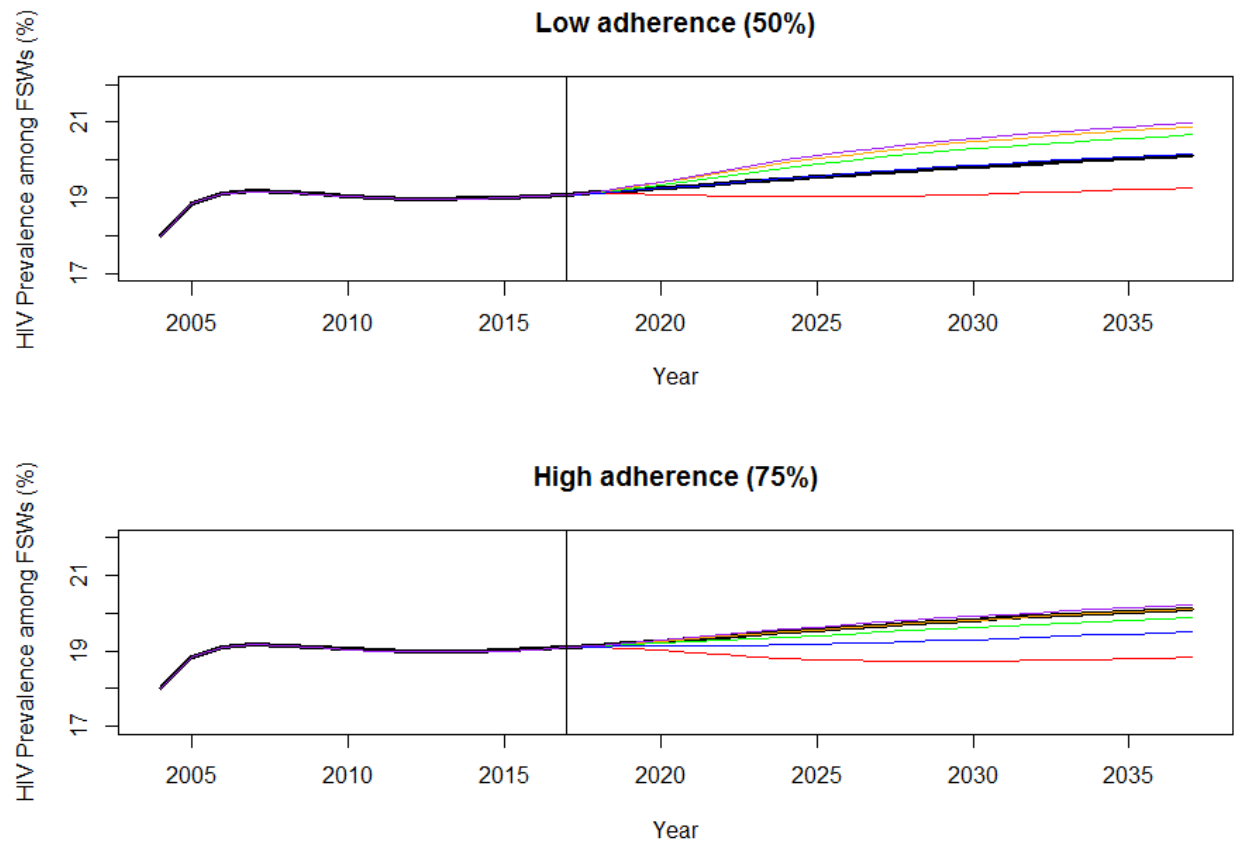
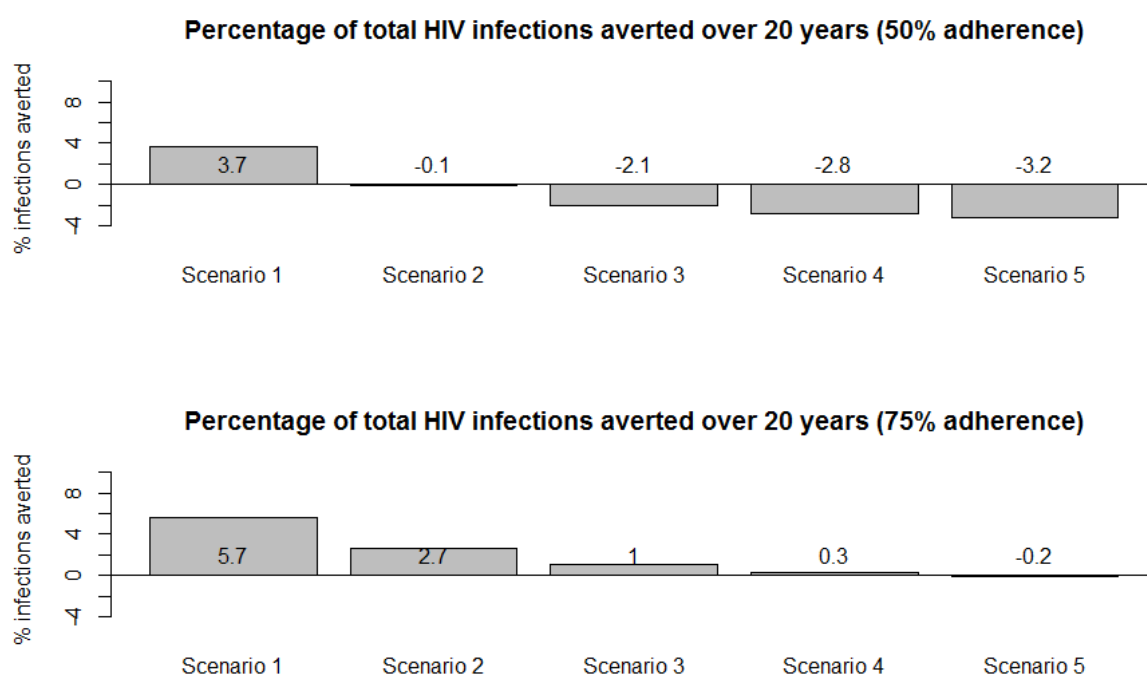


Figure 3: Percentage decrease in HIV infections amongst FSWs and clients over 20 years for low and high adherence of PrEP use and different scenarios of how PrEP use affects frequency of, and condom use in, commercial sex acts



Scenario 3: Constant income hypothesis – PrEP users increase the quantity supplied

Scenario 3 (green line in Figure 2) assumes that, in addition to decreasing condom use, PrEP users also increase the quantity of sex supplied to keep income constant, reacting to the reduction in price due to the reduction in compensating differential. Under assumptions of high PrEP adherence (75%), projections suggest that PrEP will still have a small positive impact by reducing the number of HIV infections by 1% and prevalence after 20 years by 0.1 percentage points. Under the assumption of low (50%) adherence, the model suggests that risk compensation due to PrEP would lead to a 2.1% increase in the number of infections and an increase in HIV prevalence of 0.25 percentage points.

Scenario 4: Competition – Non-PrEP users increase the amount of sex supplied

Scenario 4 (yellow line in Figure 2) assumes that all FSWs operate in one competitive market, regardless of PrEP status, and that non-PrEP users increase the quantity of sex supplied. The responsiveness of the quantity of sex supplied by non-PrEP users is increased by the product of the competition coefficient Ω_j , set to 0.5 in the base case, and PrEP coverage. Condom use among non-PrEP users is set to be constant and the same as before PrEP introduction.

Assuming that competition increases the total sexual activity among non-PrEP users has a substantial effect on the estimated impact of PrEP. Under assumptions of high adherence, PrEP introduction is estimated to lead to a 0.3% decrease in the total number of HIV infections over the 20-year time horizon. However, lower adherence assumptions project a more pessimistic scenario where PrEP introduction is projected to increase the total number of HIV infections by 2.8%.

Scenario 5: Competition – Non-PrEP users change the amount and type of sex supplied

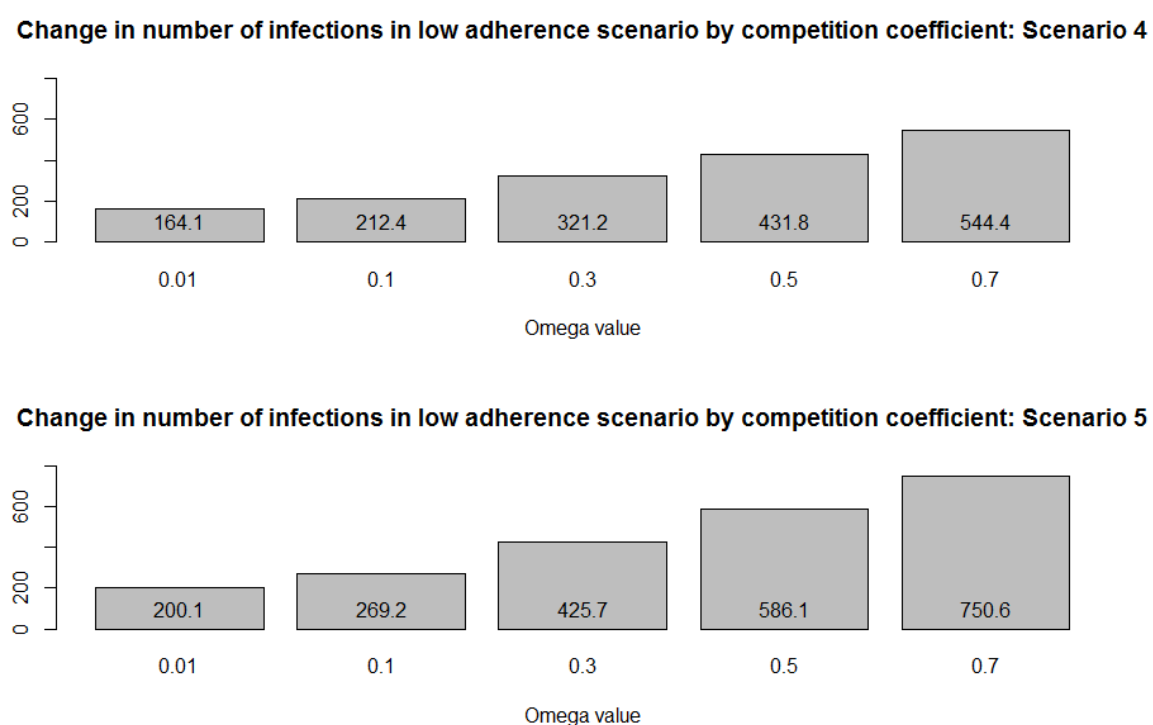
Scenario 5 (purple line in Figure 2) extends scenario 4 to assume that alongside increasing the quantity of unprotected acts supplied, non-PrEP users also reduce condom use according to the factor Ω_j and PrEP coverage. When adherence to PrEP is high (75%), increases in the quantity of acts and decreasing condom use results in a 0.2% increase in HIV infections, a 0.4 percentage point increase in prevalence. However, when adherence to PrEP is low (50%), overall HIV prevalence is estimated to increase by 0.04 percentage points, a 3.2% increase in the number of infections.

Sensitivity analysis

In addition to presenting scenarios of high and low adherence to PrEP, we conduct further one-way sensitivity analyses to examine the sensitivity of model results to key

assumptions. An important assumption behind the finding that PrEP may have an adverse impact on HIV prevalence is the assumption made about how competition in the market between PrEP users and non-users results in non-users providing a greater quantity of commercial sex acts (scenario 4) and decreasing their condom use (scenario 5) to ensure they maintain their existing earnings. In the main analyses, we assume that the competition coefficient, Ω_j , is 0.5, i.e. non-PrEP user behaviours will be affected half as much as PrEP users. For the low and high adherence scenarios, Figure 4 shows the effect of assuming different values for Ω_j on the impact of PrEP, in terms of the relative number of infections averted resulting from PrEP introduction. We find that, even when the effect of competition is very low (e.g. $\Omega_j = 0.01$), introducing PrEP may have an adverse impact.

Figure 4: Variation in adverse impact of PrEP according to competition coefficient



Nb. The higher the number, the higher the number of HIV infections

Discussion

These results suggest that the impact of PrEP in reducing HIV infections will be highly sensitive to risk compensatory behaviours, including those driven by changes in economic incentives in sex work. The externalities of risk compensation among PrEP users, which we assume to influence the behaviour of non-PrEP users through participation in a single competitive market, are estimated to be particularly important to the effectiveness of PrEP. In line with other modelling studies, PrEP impact is highly dependent on adherence assumptions.

This study is not intended to be a precise representation of a particular HIV epidemic or of how economic incentives could affect the impact of PrEP. These results will not perfectly predict the impact of PrEP, nor behavioural responses to its introduction. However, results are striking in the magnitude and implications of their predictions; specifically, that the impact of PrEP may be negated by risk compensation among PrEP users, consistent with evidence from economic research. In addition, when externalities of risk compensation are considered such that behaviours of non-PrEP users are influenced by those of PrEP users, this study suggests that introducing PrEP may have a negative overall impact, resulting in an increase in HIV infection transmission. Importantly, this is most likely if PrEP is being used with low adherence such that it has low efficacy.

To-date, no studies have considered the effect of PrEP – or other preventative interventions – on the economics of sex work. A broad range of data are collected during trials and demonstration projects of HIV prevention products, which offer the opportunity to gather revealed preference data on the extent of risk compensatory behaviours. However, these studies do not generally collect data from FSWs who are not using PrEP, and are often dependent on self-reported condom use which can be biased. The results of this analysis demonstrate that changes in the behaviours of non-PrEP

users may be important in maximising the impact of PrEP programmes. Further research is needed to assess the real-world impact of interventions on the economics of sex work and how that then effects the behaviour of all FSWs, including, but not limited to, the extent that financial incentives for risky behaviours are modified by interventions.

We do not consider changes in the demand side of the market. All scenarios assume perfect competition with unlimited demand for condomless sex among clients, where changes in individual supply do not affect demand, whilst the market continues to clear by reductions in price. An alternative interpretation, which we do not address in this paper, would consider demand for unprotected sex finite and satiated before the introduction of PrEP. In this case, the PrEP would not lead to an increase in supply of unprotected sex, however may lead to an increase in the supply of protected sex as FSWs maintain a constant income. Since this analysis relies on the price of protected sex remaining constant, we are unable to explore this further. Conversely, if protected and unprotected sex are substitute goods, a reduction in price for unprotected sex may lead to a reduction in the price and quantity supplied of protected sex, meaning that we overestimate the extent to which PrEP's impact is reduced.

This paper makes a number of assumptions which may not hold in reality. Firstly, risk compensatory behaviours among FSWs are predicted through the analysis of stated preference DCE data and may suffer from hypothetical bias. Although systematic review evidence suggests that the predictive ability of DCEs is reasonable[42]¹⁴, they are thought to over-predict desired behaviour changes, and underestimate undesirable behaviour[64, 65]. Therefore, this analysis may overstate the responsiveness of FSWs to price changes, predicting greater risk compensation than might be observed in reality.

Secondly, we impose a restrictive model of the market for commercial sex. Demand is assumed to be constant. Although PrEP use is likely to be unobserved by clients, FSW

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revelation of use could signal her HIV negative status alongside a willingness to protect her health. This signal that an act may be safer could increase a client's willingness to pay for unprotected sex, increasing incentives in the provision of unprotected sex. Also, FSWs may also exhibit risk compensatory behaviour if they are HIV positive and on HIV treatment; one study in Senegal finds that condom use among persons using ART is lower than that among HIV negative or HIV positive persons not on treatment[26].

In addition, if client preferences are augmented by actual or perceived FSW PrEP use, the market may become segmented such that clients only purchase sex from PrEP users or non-users, and do not operate in a single market as modelled here. This would reduce the impact of externalities among non-PrEP users, and mean we underestimate the impact of PrEP in scenarios 4 and 5. However, the extent to which FSWs might want to, or could, reliably signal PrEP use to clients is unclear.

Scenarios 3, 4 and 5 use the target income hypothesis to justify the assumption that FSWs set a weekly income target. This assumption is different to a classic dynamic model of labour supply which predicts that people will work less when wages fall, due to a lower opportunity cost of leisure time[66]. Although multiple studies have found evidence of this reference dependence in labour supply [23, 61, 62, 67] and research has repeatedly shown weak or insignificant evidence of this [68-70], there is some studies have demonstrated behaviours consistent with the classic model of labour supply[71].

We do not use economic theory when modelling changes to the extensive margin, or entry to and exit from, sex work. Instead we use standard assumptions of transmission modelling to retain a fairly consistent population size, minus HIV-related mortality. If wages fall after the introduction of PrEP, the benefits of a career in sex work in the form of financial earnings far greater than available in other areas of the economy, may be substantively reduced. In this instance, we would expect the number of new HIV negative entrants to sex work to reduce.

This model only considers changes to HIV transmission, and does not consider other STIs or unintended pregnancies. New HIV prevention products are generally single-purpose, and only prevent HIV transmission, yet condoms are multipurpose products which confer protection from unintended pregnancy and other STIs. Substitution from condoms to a single-purpose product may result in additional health losses from these, which are not accounted for here. In addition, DCE data have shown that other attributes of HIV prevention products may be more attractive to some FSWs than HIV prevention, including additional protection from unintended pregnancy or STIs.

Conclusion

This paper raises the question of how prevention interventions may affect the economics of sex work and so have other unforeseen effects. It shows how the impact of a new HIV prevention product, pre-exposure prophylaxis (PrEP), may be reduced by changing the supply-side economics of commercial sex. This study is the first to explicitly incorporate economic factors, which have elsewhere been demonstrated to affect the behaviours of FSWs and clients, into a dynamic HIV transmission model. Through using stated preference data and behavioural economic theory, we model the possible effect that risk compensation among FSWs may have on the impact of PrEP in reducing HIV infection. We find that existing models may substantially overestimate the impact of PrEP where they do not account for risk compensation among users, in terms of the quantity and type of sex acts they engage in. Results indicate that ensuring high (>75%) adherence to PrEP will be critical in achieving a substantive impact on HIV transmission.

This study explores a number of hypotheses which merit further investigation, ideally with high-quality observational data collected among both PrEP users and non-users. In particular, results suggest that economic factors might mitigate the impact of PrEP interventions, yet act-level data on price or other dynamics are rarely collected in PrEP demonstration or implementation projects or their process evaluations. Few data are

also collected among FSW groups who are not engaged with clinical trials or demonstration projects, yet longitudinal data on economic factors will be essential to fully explore the impact of HIV prevention interventions. Further work is also needed to counter potential biases in the reporting of prevention interventions, including condoms.

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Supplementary Table S1: Potential measures of condom use in primary survey carried out in South Africa in 2015

Survey question	Inferred condom use parameter
Reporting that a condom is <i>always</i> used in commercial sex acts	96%
Reporting condom use a last sex (commercial or otherwise)	91%
Reporting an amount when asked on average how much she sells unprotected sex for	78%
Reporting knowledge of other FSWs who provide unprotected sex	60%

Conclusions from paper R4

This paper explores how a new HIV prevention product, referred to here as generic PrEP, could affect the economic environment of sex work and change the behaviours of FSWs. It found that risk compensation among FSWs, attributable to changes in the economics of sex work, may have a substantive negative impact on the population-level benefits of PrEP products.

This paper has a number of limitations. Risk compensation is predicted from DCE data, which were shown in the systematic review of chapter 4 to be at risk of incorrectly predicting the sensitivity of individual choices to changes in the choice environment. Furthermore, it is not calibrated to a particular HIV epidemic in sub-Saharan Africa, although South African data is used from the primary fieldwork of this thesis. This, coupled with the fact that the model is a simple characterisation of the epidemic, may mean that some inferences may not be robust.

However, although the empirical results of this paper may not be precise, the predicted effect of risk compensation on the impact of PrEP is indicative that more research is needed to investigate the potential adverse effects resulting from PrEP introduction and use. In particular, data is needed from FSWs who choose not to uptake PrEP products to explore if behavioural externalities, which we model based on theoretical expectations, may impact behaviour in reality.

Chapter 10: Discussion

This thesis set out to assess the potential impact and cost-effectiveness of new HIV prevention products by eliciting the stated preferences of men, women, adolescent girls, and FSWs. This chapter provides a critical assessment of the major findings of the thesis, notes their strengths and limitations, and discusses their implications for research and policy. This chapter meets research objective 5, to identify key findings from this thesis and discusses the implications for the introduction of HIV prevention products

Major findings

This section summarises key results arising from this thesis, presented according to the objectives outlined in chapter 1.

Objective 1: To quantify the determinants of demand for new HIV prevention technologies among adult men, women, and adolescent girls in the general population, and female sex workers

The first objective was addressed in paper R1, where a DCE with 661 self-reported HIV-negative respondents found that the largest determinant of product demand across all groups would be HIV efficacy. We also found strong preferences for MPTs, with pregnancy and STI characteristics important to the choices of all groups. However, less promising for the HIV response among AGYW groups, evidence from MNL and MMNL models respectively suggested that adolescents find the intravaginal ring and oral PrEP intrinsically less appealing products compared to other women.

However, this paper also identified some promising areas for HIV prevention moving forward. All four groups displayed strong preferences for injectable PrEP products, while the minor side-effects included in the DCE were not important to respondents. Perhaps most importantly, latent class results suggest that products offering

multipurpose protection would be desirable to younger women and FSWs, who displayed weaker preferences for single-purpose HIV protection products.

Objective 2: To estimate the impact and cost-effectiveness of new HIV prevention products among South African men, women, adolescent girls, and female sex workers

The second objective was addressed in paper R2, where a cost-effectiveness analysis showed that a range of candidate multipurpose HIV prevention products would likely be cost-effective if introduced among younger women (aged 16-24) or FSWs but are unlikely to be cost-effective if introduced among older women (aged 25-49). Roll out scenarios that included one or more MPTs were predicted to be slightly more cost-effective than scenarios of single-purpose products for two reasons. First, MPTs were predicted to be more attractive to potential users, leading to greater uptake and economies of scale from product use. For example, we predicted that product uptake among women under 25 would be 8% for a range of single-purpose products, but that uptake would increase by 27 percentage points to 35% for a full range of MPTs. Second, the costs associated with averting unintended pregnancies reduced the net costs of the intervention and led to greater benefit through averting maternal mortality.

The impact model used in this paper is relatively simple; however, its results are broadly comparable to published studies estimating the cost-effectiveness of single-purpose PrEP[1]. In a series of one-way sensitivity analyses, we tested the sensitivity of this model to qualitatively important parameters and found the results sensitive to assumptions of HIV incidence, product adherence, and the coverage of ART. This paper strengthens the evidence for continued investment in MPTs to improve sexual and reproductive health.

Objective 3: To assess whether HIV prevention products will change female sex worker preferences for the supply of condomless commercial sex

The third objective was addressed in paper R3, where a repeated DCE with two different framings found that PrEP could markedly change the supply side of the commercial sex market. We predict that PrEP use would lead to a substantial decrease in the condom differential, the price premium for unprotected sex, by 73% due to an increase in utility provided by the fee for an act and a parallel decrease in the utility provided by condoms. Notably, simulations from DCE data indicate that the quantity of condomless sex supplied could more than double, increasing by a factor of 2.3. There was no significant heterogeneity in the impact of PrEP on supply. However, there was some evidence of market segmentation, and this may have been due to the small sample of HIV-negative FSWs identified.

Objective 4: To explore if changing incentives in sex work could substantially affect the impact of HIV prevention products through risk compensation

The fourth objective was addressed in paper R4, which used the results of the FSW DCE to explore if changes in the economics of sex work due to the introduction of an effective HIV prevention product could substantially reduce their impact through risk compensation. This paper combined an epidemiological dynamic transmission model of HIV with microeconomic theory and found that 1) the impact of PrEP is likely to be highly dependent on adherence; and 2) the extent of competition among PrEP users and non-users – particularly how much behaviour change among users is replicated among non-users – could substantively affect the overall impact of PrEP. Although the model was not parameterised for a specific HIV epidemic, the substantive changes in estimates of PrEP impact attributable to risk compensation due to economic factors indicate that more research is needed in the area.

Objective 5, to identify key findings from this thesis, and discuss the implications for the introduction of HIV prevention products, is met by this discussion Chapter.

An additional methodological objective was:

Objective 6: To assess the reliability of discrete choice experiments to predict health-related choices

A systematic review (chapter 4) sought to validate the application of DCEs in this thesis, specifically assessing their accuracy in predicting health-related behaviours. The review identified eight studies that met the inclusion criteria, where individual-level stated and revealed preference data were captured for health choices. A meta-analysis pooled the results of these studies using a bivariate mixed-effects model to account for the co-dependency between measures of sensitivity and specificity.

We found that DCEs have reasonable accuracy when used to predict behaviour with a sensitivity of 88% (95%CI: 81%, 92%) and a specificity of 34% (95%CI: 23%, 46%). This means that when a DCE suggests that somebody *will* behave in a certain way (for example, opting for a treatment or programme), this may be a more reliable statement than if it suggested that somebody *will not* behave in a certain way (for example, they will not use a treatment or programme).

Although low compared to the accuracy of diagnostic tests, these figures indicate that DCEs can be useful tools when other forms of prediction are inaccurate or unavailable, such as in the early stages of product introduction. The low number of studies assessing the validity of DCEs means that we conclude that substantial additional work is required in the area, particularly to explore heterogeneity in results.

Contribution to knowledge

The contribution to knowledge of this thesis can be summarised in terms of those of empirical findings, and those of methods.

Contribution of empirical findings

This thesis contributes knowledge to inform the development and roll-out of ARV-based prevention in South Africa. A key finding of paper R1, that female groups find oral PrEP

or intravaginal ring products less appealing, is particularly important because emergent HIV prevention initiatives, such as the DREAMS programme in South Africa[2], are investing substantial resources to the scale-up distribution of these products among AGYW. Large-scale spending on products that potential users will not find attractive will likely lead to misallocation of scarce resources, a particular concern when donor spending on HIV is forecast to decrease in the short to medium term, exacerbating the opportunity cost of decisions[3].

Taken together, papers R1 and R2 show the value of including end-user preferences in programme planning and modelling. Assuming the predictions of the DCE are valid as shown in chapter 4, at least for estimating relative uptake between groups, results show that heterogeneity in preferences across populations is likely to impact cost-effectiveness estimates to some extent. Also, the sensitivity analysis of paper R2 showed that variation in predicted uptake is likely to have a relatively small effect on cost-effectiveness when compared to other factors - particularly assumptions relating to incidence in different groups and scale-up of ART.

Importantly, papers R1 and R2 strengthen the economic case for the scale-up of oral PrEP among South African AGYW populations, in addition to FSWs among whom it has recently been introduced[4]. Aside from increased economies of scale where fixed costs are divided among a greater number of users, the high HIV incidence among younger women means that we predict single-purpose oral PrEP and intravaginal rings to be cost-effective in this group, despite the ring having a very low demand among AGYW. However, the latent class model in paper R1 predicted that younger women were less likely to value HIV prevention in a product than older women. To achieve high PrEP coverage, and therefore cost-effectiveness, among this group, efforts should be made to motivate uptake and encourage adherence. Predictions of cost-effectiveness despite a comparative dislike of the ring and oral PrEP products suggest that, if these products

could be made more attractive to younger users, increases in uptake and use could improve their cost-effectiveness.

In papers R3 and R4, our attention turned to the implications of introducing PrEP among the FSW population. Paper R3 details the results of a DCE, the first to be carried out among FSWs to-date, which indicates that PrEP could have a substantive impact on the economics of commercial sex, decreasing the price premium for condomless sex and potentially increasing the quantity of condomless sex supplied. This is also the first study to explore the impact of new HIV prevention products on the economic aspects of commercial sex work, filling the gap in the economic literature that does not consider how new prevention products will change incentives in commercial sex work.

In line with the general approach of this thesis, paper R4 extends the use of DCEs beyond their current application where, in combination with key findings from microeconomics, results are used to better inform epidemiological models of PrEP impact. Until now, epidemiological transmission models have made zero, or arbitrary, changes to parameters simulating risk compensation under PrEP use (e.g. [5-7]). This study is the first to formalise a risk compensation framework based on widely-accepted and empirically evidenced economic theory, albeit not in commercial sex.

In doing so, this study takes the economically significant findings from paper R3, extrapolates from the surrogate outcome of condom substitution to impact on the HIV epidemic, to suggest that condom substitution due to changing economic factors may have substantial epidemiological importance. We also find that ensuring high adherence to PrEP will be critical to maximising impact. Interestingly, paper R4 highlights how even small changes to the behaviour of non-PrEP users, as a plausible result of competition, may reduce or negate impact. Few data are currently captured among FSWs who are not participating in a PrEP trial or demonstration project. To validate (or refute) the stated

preference evidence in this thesis, a broader range of data must be collected from non-users.

Taken together, results from papers R2 and R4 highlight the importance of using high-quality end-user data to maximise the impact and cost-effectiveness of interventions. Importantly, the sensitivity of the cost-effectiveness and dynamic transmission models, used in papers R2 and R4 respectively, to adherence parameters indicate that investments in interventions to enhance consistent product use are likely to be cost-effective. Ideally, programmes supporting uptake and adherence would be designed using reliable end-user data, such as that obtained from DCEs.

Contribution to methods

An important methodological contribution of this thesis is to apply DCEs to inform uptake parameters in an economic evaluation. Paper R2 is one of the first published examples of DCE use for this purpose in any health context and the first in the HIV field. As found in the systematic review exploring the predictive ability of DCEs in chapter 4, DCEs are imperfect tools for prediction. Yet when compared to alternatives of expensive trials or obtaining expert opinion, we have argued throughout that they may be less biased and allow a greater understanding of the heterogeneity of uptake within and across different groups. Chapter 4 is the first systematic review to synthesise evidence of the predictive ability of DCEs in health and provides an evidence base for their further use in the absence of alternative predictive methods.

An additional methodological contribution is the integration of a microeconomic model of behaviour within an infectious disease model. To date, models of interventions among FSW have used arbitrary changes in assumptions to assess the sensitivity of models to behavioural responses to interventions, such as condom substitution. Also, although many models carry out one-way, two-way, and probabilistic sensitivity analyses, none

were identified which co-dependently varied the rate of condom use and the number of commercial acts supplied, the key prediction from the empirical findings of paper R3.

Finally, to my knowledge, these DCEs are the first to be carried out among a FSW population. When gathering data among FSWs, flexibility is required in many survey methods including sampling strategy, considerations of confidentiality, and arrangements for interviewer and participant safety. Yet, the successful implementation of both DCEs among the FSW sample shows that they can be useful tools to elicit the preferences of this group.

Limitations of thesis approach

The strengths and limitations of specific methodological and analytical approaches have been discussed in the preceding Chapters. Therefore this section focuses more on overarching themes.

Modelling as a simplification of reality

The modelling of complex phenomena, such as the spread of HIV in a population or the costs required to reach populations at risk, require necessary simplifications of reality. The models employed in this thesis were designed with the aim to identify and explore the impact of important factors thought to influence the HIV epidemic, for example estimating the differential impact of interventions in older and younger women. In addition, due to requiring assumptions around important parameters such as effectiveness or adherence, *ex-ante* impact and cost-effectiveness models may be less-robust than *ex-post* evaluations which are able to incorporate more certain observational data. Sensitivity analyses are included in papers R2 and R4 in an effort to mitigate the impact of parameter or methodological uncertainty. Nevertheless, these cost and impact models are likely to have omitted important factors which may substantively influence results.

For example, assumptions around adherence to PrEP has been shown to be a critical factor in both observational and modelling studies, e.g. [1, 8, 9]. In this thesis, adherence is included in both models through linear reductions in the product efficacy parameter, yet this may not accurately reflect the complexity of adherence in reality. For example, an individual may use ARV-based prevention products adherently for short periods of time when they consider themselves to be at risk, and not at all at other times. In another scenario, a proportion of users might use PrEP perfectly adherently while others never use a product. Separate compartments would be required to model this, with an understanding of the interaction between other factors and the likelihood of high adherence. Data are not yet available for adherence patterns to ARV-based prevention (some research has been carried out on adherence to ART[10]), though we can expect the determinants of adherence to be heterogeneous across users.

The FSW DCE and model in papers R3 and R4 aimed to predict risk compensation among FSWs, specifically the provision of more unprotected sex if they were to initiate effective HIV prevention. The behavioural response to PrEP initiation is also likely to be heterogeneous, and likely correlated with socio-economic circumstance or FSW bargaining power. The DCE did not detect any differential response to PrEP introduction by observable characteristics, yet the main interaction effect was only marginally significant, and it is likely that the DCE was underpowered to detect these differences. If some FSWs are highly responsive to the introduction of PrEP, and some are not, it will be important to understand which women need additional support in maintaining consistent condom use with commercial partners.

Imperfect analytical and predictive ability of DCEs

Chapter 4 presents the first systematic review of the predictive ability of DCEs in health, and although it shows that DCEs give reasonable predictions of real-world behaviours, the number of included studies was very small and estimated sensitivity and (in

particular) specificity values low. Yet the use of DCEs in this thesis was motivated by a desire to obtain objective, rapid, and relatively inexpensive data on the preferences of different populations towards HIV prevention products, and predictions are presented with this caveat in papers R2 and R4. These were the first DCEs to be carried out among FSW populations, while very few have been conducted among persons under the age of 18. The consistency of results with prior expectations suggests that the internal validity of DCEs holds within these populations. However it would have been optimal if stated preference data could have been combined with revealed preference data obtained from PrEP trials or demonstration projects.

On reflection, closer collaboration with ongoing PrEP projects based at Wits RHI could have provided this data. However, the delays in the early stages of this project meant that data collection in the TAPS demonstration project began before we had sufficiently strong collaborative links with the institution to suggest the collection of economic data. I hope to investigate this in postdoctoral work.

We aimed to reduce hypothetical bias in both DCEs by engaging in extensive piloting and testing, and by including opt-out alternatives in the final design. This approach should have enhanced the process validity of the DCEs, while the direction of coefficients was broadly in line with *a priori* assumptions, further supporting the theoretical validity of findings.

Nevertheless, erroneous predictions due to hypothetical bias may have important implications for using DCE predictions, particularly if they over-predict demand. Over-prediction would bias the results of paper R2 towards being more cost-effective and therefore potentially problematic for the method. Although Lancsar and Swait[11] suggest that DCEs predict fairly well outside of the health field, they suggest that the inconsequentiality of choices in health DCEs may exacerbate hypothetical biases, or that the reduced form choices presented in DCE tasks omit key features of choices which may

be important to respondents. We are unable to assess this with the stated preference data collected for this thesis.

Design decisions for both DCEs were taken with the aim of detecting statistically significant effects among attributes. This meant that potentially important attributes, or interactions between attributes (for example the risk and duration of side-effects), were considered but ultimately left out. On reflection, this may have been an excessively cautious approach given the use of efficient designs, our large sample sizes, and the number of significant parameters in the main effects models of both DCEs.

Reliance on self-reported data

Due to financial and human resource constraints, we were not able to collect biomarker data to objectively assess HIV or treatment status and we relied on participants accurately self-reporting their HIV status, sexual behaviour, and other sensitive information. Self-report is a quick and cost-effective means of collecting data. However, the validity and completeness of self-reported sexual behaviour data is unclear at best [12-15].

Often self-report is often the only way to obtain individual-level data on important sexual behaviours. Based on best practice developed by the UK's National Surveys of Sexual Attitudes and Lifestyles (NATSAL) [16, 17], we took steps to minimise reporting bias during data collection: 1) our fieldwork team comprised solely of interviewers with prior experience of collecting sexual behaviour data from general population groups; 2) extensive training was led by specialist researchers at the University of the Witwatersrand to enhance the capturing of data around intimate partner violence and condom negotiation; and 3) surveys were coded into tablet computers in an accessible manner to allow participants to answer directly on the tablets themselves, rather than have to reveal information orally to an interviewer.

Despite this, self-reported HIV prevalence was lower in the general population than in national representative surveys[18], and lower among FSWs than other RDS surveys[19]. Reported condom use at last sex was also higher among all four populations in this survey than others (ibid.). These data indicate that that acceptability biases may have led to the misreporting of HIV status and other sensitive behaviours. For the modelling work in this thesis, we attempt to mitigate this bias by taking the majority of parameters from representative studies (such as the South African Health Science and Research Council surveys[18]), which capture biomarker data in addition to self-reported information.

Time and resource constraints in fieldwork

Fieldwork was initially planned to take place over 15 months from September 2014 to December 2015. However, staff movement and administrative delays in our collaborating institution meant that ethical approval for piloting work was not obtained until August 2015. Although a great deal of the survey implementation work was front-loaded, including the design and programming of pilot tools and the recruitment and training of interviewers, the reduction in project time from 15 months to 5 months meant that some planned activities had to be dropped. For example, the products DCE was designed without primary FGD work to identify attributes and, instead, we used FGD data from a similar DCE carried out by the primary supervisor of this thesis in 2005. Nevertheless, we managed to protect the three-month window allocated to quantitative data collection, and ensure that the quality of interviews and sampling methods was not reduced by time constraints.

Strengths of thesis approach

Combination of economic and epidemiologic methods

Perhaps the key strength of this thesis is the formal integration of economic methods into infectious disease models. This approach allows us to objectively consider

complexity in model parameters, specifically variation in prevention product uptake and condom substitution estimates, and offers a greater understanding of potentially important nuances in estimating the impact and cost-effectiveness of ARV-based HIV prevention products.

The uptake predictions used in paper R2, derived from DCE results, suggest that uptake of an MPT product among AGYW would be three times that of a single-purpose product. Although previous research has identified unmet contraceptive need among this group [20], there has been limited work to estimate the incremental demand that an MPT could command. The integration of end-user DCE data into a cost-effectiveness model meant that we were able to explicitly model the cost-effectiveness of MPTs, accounting for the heterogeneity in demand for contraceptive characteristics that we observed across female populations.

Paper R4 also uses the results of a DCE to inform a mathematical model and is the first to incorporate an explicit economic model of behaviour in the estimation of key parameters. Economic theory describes how people trade off risk and reward in labour markets, which is useful in modelling shocks to a market such as the introduction of PrEP. Yet, despite evidence that economic factors can strongly influence FSW and client behaviours, noted in the earlier systematic review, to-date mathematical models have not incorporated these factors when modelling HIV transmission in the market for commercial sex.

South Africa as a research context

South Africa was chosen as a study site for this research for a number of reasons, including strong institutional links between LSHTM and Wits RHI, and research capacity in the data collection team. Moreover, the high HIV prevalence in South Africa, alongside the proven political and social acceptability of ARV-based HIV prevention methods, means that the results of this thesis have the potential to contribute to discussions on

how to implement PrEP or develop MPTs for South African users. South Africa is also a comparatively wealthy country in sub-Saharan Africa, and is aiming to integrate health technology assessment in its decision making in the medium term [21]. This may make the cost-per-DALY averted estimate in paper R2 more applicable here than in other contexts, where health decisions may be less likely to be explicitly made incorporating a transparent health economic framework.

Due to its profile and status at the forefront of the epidemic, there has been a wealth of economic and infectious disease modelling work carried out in South Africa in recent years. Although this reduces the scope for novelty in this thesis, a large quantity of high-quality health and economic indicator data are available (and have been used in this thesis) to aid in these research efforts. As such, in the models presented here, we have been less reliant on self-reported data to parameterise inputs than we would have been in other countries. Additionally, we were able to compare the results of these models to existing, accepted studies and assess the implications of the innovations in considering a) MPT products and b) changes in behaviour due to risk compensation.

Finally, although residents of certain areas of Johannesburg have been inundated with requests to participate in HIV trials, surveys and programmes, by travelling 30km South-East of the city centre for fieldwork we were able to reach a relatively research naïve population (except for the 2005 DCE by the supervisor of this thesis, which was also partly carried out in Vosloorus township). This meant that, although interviewers had to spend a large proportion of interview time introducing the new products and discussing how they work, the preference data we gathered are less likely to be influenced by previous participation in HIV prevention research.

A new perspective on multipurpose prevention technologies (MPTs)

Although research on candidate MPT products has previously identified an unmet need for effective, female-initiated products (e.g.[14, 22-25]), just one study has assessed the

potential cost-effectiveness of an MPT[26]. A strength of this thesis is the use of robust economic evaluation methods to assessing the cost-effectiveness of different MPT rollout strategies among a range of population groups. The results of the DCE and this study have been of particular interest to the MPT advocacy community, and the author has since presented a webinar for the Initiative for Multipurpose Technologies (IMPT).

Data quality and generalisability to other settings

The randomised sample of general population participants means that we can be relatively confident in generalising the findings of the DCE to other urban and peri-urban areas of South Africa. After applying sample weighting, our sampled showed reasonable similarity in background characteristics to other surveys of the South Africa population. That said, contextual factors may limit the extent to which findings can be generalised, as there is huge racial heterogeneity within and across administrative areas in South Africa.

The RDS sample among FSWs used best-practice methods to obtain 203 interviews with the hard-to-reach population. Because of the low prevalence of sex work in the general population, RDS methods enabled a targeted, snowballing approach to be deployed to reach a sufficient sample size. Survey weights were then used to quantitatively adjust results to make results generalisable to the FSW population. As noted in the results papers, RDS methods do not entirely mitigate the sampling biases introduced by RDS, and a number of assumptions are required for data to be representative to all FSWs. Even then, the heterogeneous nature of sex work contexts in South Africa means that generalisability may not even be possible for sex work locations geographically close to data collection. Nevertheless, since the alternative approach would be to simply analyse data collected among a snowball sample, the RDS adjustment is preferable.

Implications for research

This section considers the broad research implications of this work, alongside its generalisability to other settings.

Implications for the further development of MPTs

In April 2017, during the writing up stage of this thesis, the International Partnership for Microbicides (IPM) initiated a phase 1, randomised trial of the pharmacokinetic and safety characteristics of a multipurpose HIV and contraceptive Dapirivine/Levonorgestrel vaginal ring (MTN-030/IPM 041)[27]. Although this is a promising step towards the development of an effective MPT option in LMICs¹⁵, the results in paper R1 suggest that it would be optimistic to assume that a ring-based MPT will be an attractive option for younger women, yet potentially cost-effective as demonstrated in paper R2.

Instead, results from this thesis suggest that future research should focus on the development of alternative MPT modalities, particularly injectable products. Also, more research is needed on the short- and medium-term opportunities that co-provision of individually produced and regulated products could have. Although MPTs were described in the products DCE as co-formulations, there is no evidence suggesting that co-provision would be less impactful.

Alternatively, while this thesis shows what can be done with relatively little hypothetical choice data, this is no substitute for a well-powered, observational study of revealed preference product uptake. It is essential that the uptake of single- and multi-purpose products be monitored throughout phase III trials and early implementation studies to ensure that they have the potential to meet end-user expectations.

¹⁵ IPM owns the exclusive licence for Dapirivine from Janssen Sciences Ireland UC, an arrangement that aims to ensure that women in low-resource settings have affordable access to effective, topical HIV prevention

Finally, rigorous assessment of the cost-effectiveness of candidate MPT products is needed to ensure that resources are efficiently allocated as MPT products become available. It is likely that the pharmacokinetic and regulatory barriers to MPT introduction will result in a high unit cost, which may or may not be fully passed on to purchasing governments or individuals. In the short to medium term, co-provision of HIV preventative and contraceptive products may be one option to capture the potential benefits of MPTs.

Health systems in high HIV burden countries are likely to have notably limited resources, and purchasing MPTs, or single-purpose prevention products, is likely to require disinvestment from current health spending. As South Africa moves towards implementing formal HTA processes, the quality of the economic evidence for MPT introduction will face increased scrutiny, and it is important that economic evaluations meet as many of best-practice criteria as possible, for example, those in the Bill and Melinda Gates Foundation Reference Case [28].

The case to consider unintended consequences of introducing ARV-based prevention among FSWs

The optimism in research and advocacy groups for ARV-based prevention interventions to reduce HIV incidence among FSW groups is not unfounded, and PrEP trials and demonstration projects among FSW have shown encouraging acceptability and adherence results[29]. Yet this work demonstrates that maximising the impact and cost-effectiveness of interventions may be more nuanced than currently considered in the epidemiological literature. Drawing from a large body of economic research into sex work, until now not considered by impact models, paper R4 shows that a relatively simple model predicts that the impact of PrEP could be substantially, or entirely, mitigated by economic influences in sex work.

For such unintended consequences to be measured and fully considered, data needs to be captured by PrEP implementation programmes on potential areas of risk compensation, including changes in the quantity, type, and price of sex supplied to different cadres of clients. Where possible, innovative techniques should be used to minimise desirability biases in responses, for example, list randomisation methods [30, 31].

Paper R4 also demonstrated the importance of measuring the impact of interventions among non-recipients, particularly when risks emerge from competitive market equilibria such as in sex work. Although difficult to do, capturing data from non-users has three benefits: 1) exploring why some users do not uptake products; 2) enabling the use of more robust impact evaluation methods (e.g. difference-in-differences approaches) in estimating intervention impact, and 3) monitoring potential externalities from behaviour change among PrEP users.

Implications for policy

Not all products will be attractive to end-users

Although this thesis shows that there is likely to be demand for effective HIV prevention products, not all population groups display the same preferences, and contraceptive properties are likely more desirable among some groups than others. As shown by the comparative failure of microbicide trials, largely due to poor adherence[9], it is critical to understand which products will be most effective in different contexts. When more than one ARV-based prevention modality is available, as is likely in the near-term due to successful trials of the intravaginal ring[32, 33], careful consideration is needed to 1) ensure that the right products are made available to different population groups, 2) that products are not withheld from potential users due to their demographic or risk profile, and 3) that effective adherence support is provided to users to encourage consistent and

effective product use. Condoms remain an important tool in HIV prevention programming

Although condom substitution was shown in paper R4 to potentially mitigate the beneficial impact of PrEP among FSWs, paper R2 found that MPTs were largely cost-effective under assumptions of 51% condom substitution; although this model does not consider the direct or indirect impacts of other STIs. If condom substitution is minimised among product users, the impact cost-effectiveness of new single- and multi-purpose technologies will be improved.

South Africa guidelines for PrEP and LARC use explicitly recommend the continued use of condoms alongside other preventative technologies; however the results of this thesis suggest that this recommendation must continue to be highlighted in guidelines and clinical practice. As with existing imperfect prevention methods, such as VMMC, consistent and continued information provision is required to ensure that product users understand the extent to which they are (and are not) protected from HIV and unintended pregnancy, and explicitly that they are not protected from many STIs when using non-barrier methods.

The need for innovative programming for HIV prevention among FSW and AGYW groups

This thesis has demonstrated that making effective HIV prevention products available to FSWs may not be sufficient to reduce HIV incidence and indicates that more innovative programming may be needed.

Among FSWs, papers R3 and R4 show that financial incentives could reduce the impact of products through risk compensation, as FSWs increase their supply of unprotected commercial sex to keep income constant. One option to reduce the financial pressures on FSWs to reduce the supply of unprotected sex is to enhance risk-coping mechanisms

in the form of conditional cash transfers (CCTs) or increased access to credit, savings, and insurance products.

One CCT has been carried out among FSWs, the RESPECT II pilot study in Tanzania, with financial incentives given to FSWs conditional on remaining without an STI, yet final results have not been published[34]. Research among male sex workers in Mexico found a strong rationale for a CCT to reduce sexual risk taking [35], based on similar risks associated with the availability of higher wages for unprotected sex. CCTs have been carried out among AGYW groups to reduce risks attributable to transactional sex, however they have shown mixed evidence of effectiveness in reducing HIV prevalence [36, 37].

Formal risk-coping mechanisms are not available to many FSWs or AGYW, and there is no evidence examining the impact of providing these on sexual activity. Providing better risk coping mechanisms could affect the intensive and extensive margins of sex work [38]. In the general population, an association has been found between HIV prevalence and negative income shocks due to drought across 19 African countries, which the authors attribute to increasing quantities and risk in transactional sex[39]. Improved access to instruments for coping with financial risks in the general population, including among AGYW, could reduce dependence on transactional sex, and reduce HIV incidence.

The need for investment in uptake and adherence support

The importance of adherence to ART has led to a large number of studies evaluating the effectiveness of adherence-enhancing interventions[10], showing efficacy and – where assessed – cost-effectiveness. PrEP programmes have the opportunity to use the lessons learnt in treatment adherence interventions to design optimal support systems to maximise adherence to PrEP. Given the importance of adherence assumptions in papers R2 and R4 of this thesis, we would anticipate that interventions to support adherence to PrEP have a high probability of being cost-effective.

Encouraging uptake does not require the complexity of maintaining adherence over time, but some uptake-enhancing interventions – for example, financial incentives conditional on product uptake – may be considered to coerce product initiation and be ethically unacceptable. Instead, policymakers should focus on making products and the health services from which they are delivered as attractive as possible to potential users.

Conclusion

New ARV-based HIV prevention products offer promise in tackling the HIV epidemic, particularly in high-burden, generalised epidemics such as South Africa. This thesis set out to explore the preferences of end-users for new products and to estimate their impact and cost-effectiveness among different groups, accounting for risk-compensatory behaviours. It finds that products offering effective multipurpose protection would be attractive and cost-effective among younger female groups. A simple model also predicted the cost-effectiveness of products among FSWs. However, risk compensation due to changes in economic factors could substantially affect product impact. This thesis has shown the value of combining economic and epidemiological modelling methods to explore preventative behaviours in HIV. Further work is needed to accurately assess the external validity of these methods.

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Appendices to thesis:

**Using stated preferences to estimate the impact
and cost-effectiveness of new HIV prevention
products in South Africa**

Matthew Quaife

Appendix I: Published correspondence: The promise of multipurpose pregnancy, STI, and HIV prevention

The following paper, *the promise of multipurpose pregnancy, STI, and HIV prevention*, is a piece of correspondence published in *The Lancet Infectious Diseases*, which provides background on the arguments for MPT development, and the rationale for their integration with existing HIV and reproductive health programming. This paper is presented as published, and Appendix II gives evidence of Elsevier's permission for this.



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Interagency cooperation is the key to an effective pandemic response

We read with interest the Comment by Lawrence Gostin and James Hodge in *The Lancet Infectious Diseases*.¹ Although the focus of their Comment was on Zika virus, we are in agreement that for certain pandemic threats, characterising them, when appropriate, as national or global security threats can help galvanise interest and resources to mitigate the threats.

We view this from the perspective of the interface between the military and civilians under the umbrella of a whole-government approach. A large outbreak does more than cross international borders; the response requirements frequently cross interagency boundaries. Therefore, having ongoing communication and cooperation between agencies, long before an emerging threat surfaces, is paramount for preparedness and effective response. This allows us to be proactive rather than reactive. If we consider the 2014–15 west Africa Ebola outbreak as an example, decades of research cooperation by the US Department of Defense and National Institutes of Health provided a countermeasure platform from which to launch. Military-civilian cooperation with organisations such as the US Food and Drug Administration and pharmaceutical companies during the outbreak led to the acceleration of both therapeutic and prophylactic countermeasures, emergency use authorisation of diagnostics, and timely preclinical and clinical research.^{2,3} Thinking

ahead on developing containment care facilities at the University of Nebraska, Emory University, and National Institutes of Health, based on a Department of Defense model, years before the outbreak, allowed us to flip the switch when those facilities were needed at short notice.

Early cooperation not only has the potential to reduce cases during an outbreak but also can reduce the accompanying disease sequelae, such as the neurological disorders associated with Zika virus or chronic illnesses recognised in Ebola survivors.^{4,5} Such sequelae could lead to second or third order consequences, both economically and politically, that in and of themselves can be destabilising.

The views expressed herein are those of the authors and do not reflect the official policy or position of the US Army Medical Research Institute of Infectious Diseases, The Medical Research and Materiel Command, the US Army Medical Department, the Department of the Army, Department of Defense, the US Government, or the School of Public Health or University of Nebraska Medical Center.

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The promise of multipurpose pregnancy, STI, and HIV prevention

A recent Editorial in *The Lancet Infectious Diseases*¹ is right to point out the neglect in funding and focus that sexually transmitted infections (STIs) receive. Far greater financial and clinical engagement is needed to reduce the disease burden caused by STIs globally, but we argue that a vertical focus will not be an optimal use of limited resources. Instead, we encourage an integrated approach to preventing the triumvirate of sexual and reproductive health issues facing millions of women, particularly in lower-income and middle-income countries—specifically, STIs, HIV, and unwanted pregnancy.

An opportunity to increase overall protection to these sexual and reproductive health threats—by exploiting synergies in demand for protection—is emerging with the development of multipurpose prevention technologies that offer protection from HIV, STIs, and unwanted pregnancy. First, women with a strong desire for contraceptive protection, but weaker (still positive) demand for protection from STIs, could be conferred additional STI protection through use of these multipurpose prevention technologies. Furthermore, research by our group² shows that products offering more than one indication will be more attractive to potential users than single-purpose products.

Second, low adherence in high-risk women under the age of 25 years in HIV pre-exposure prophylaxis trials have raised concerns that current products are not meeting people's needs.³ Indeed, there is an increasing realisation that multiple prevention options are needed to suit the varied and challenging lifestyles of potential users. Importantly, products offering multipurpose protection have been

shown to be desirable to potential users, and estimates from a discrete choice experiment⁴ suggest uptake could be tripled in South African women through incorporating STI with pregnancy protection.

Multipurpose prevention technologies are becoming closer to reality. Products in development include chemical barriers such as intravaginal rings or injectable products, physical barriers such as new condoms or cervical caps, or combinations of chemical and physical barriers such as a diaphragm used with microbicide gel. A vaginal ring is currently undergoing phase 1 clinical trials with others soon to follow, although co-administration of contraceptive and HIV prevention products is also under consideration.⁵

It is time to take STIs seriously. However, investments in attractive multipurpose products that meet a range of sexual and reproductive health needs could have a greater effect than vertical spending on STIs. Combined with existing sexual and reproductive health infrastructures, multipurpose prevention could be much greater than the sum of its parts.

We declare no competing interests.

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Questioning effectiveness of vaccines against malaria

Lucas Otieno and colleagues¹ have investigated the safety and immunogenicity of the RTS,S/AS01 vaccine against malaria in HIV-infected children. The authors detail a detectable immune response in children who received the malaria vaccine, but did not assess the susceptibility of these children to natural malaria infection. There is a laboratory attached to my research unit in which malaria has been studied for more than 20 years.² Children can have up to 100 successive natural malaria infections (according to the laboratory's records), which shows the lack of natural immunity after infection in children. Adults have a very temporary immunity ranging from 6 months to a year, and if they live in Europe they lose this immunity. When returning to endemic countries, previously infected European residents can have new episodes of malaria.³ These episodes are particularly common, since previously infected adults who have not had malaria for years do not think they are still susceptible and therefore do not take necessary precautions against malaria.

As the period of natural immunity in people who live in endemic countries and who are confronted with regular infective bites does not exceed a few months, it would be extremely difficult for a vaccine to give lasting protection from malaria. Notably, in Otieno and colleagues' study, three intramuscular injections were administered 1 month apart to achieve efficacy. Earlier studies of this vaccine have shown only moderate

efficacy at best,⁴ making the goal of having a suitable vaccine for malaria relatively unrealistic, given the weak protection afforded by natural infection.

I declare no competing interests.

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Authors' reply

We recently reported safety results from an RTS,S/AS01 malaria vaccine trial in infants and children with HIV stage 1 and 2.¹ Although fewer malaria cases were reported in the RTS,S/AS01 vaccinated group than in the rabies vaccinated group, the trial was not powered to assess efficacy. Didier Raoult asks a pertinent question that many have asked in the course of malaria vaccine development: will an effective vaccine against malaria ever exist? Since natural immunity fades quickly, how could a vaccine provide long-term protection?

How to develop a malaria vaccine that is more effective than naturally acquired immunity—which does provide individuals living in malaria

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Appendix III: Parameterising User Uptake in Economic Evaluations: The Role of Discrete Choice

HEALTH ECONOMICS

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PARAMETERISING USER UPTAKE IN ECONOMIC EVALUATIONS: THE ROLE OF DISCRETE CHOICE EXPERIMENTS

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ABSTRACT

Model-based economic evaluations of new interventions have shown that user behaviour (uptake) is a critical driver of overall impact achieved. However, early economic evaluations, prior to introduction, often rely on assumed levels of uptake based on expert opinion or uptake of similar interventions. In addition to the likely uncertainty surrounding these uptake assumptions, they also do not allow for uptake to be a function of product, intervention, or user characteristics.

This letter proposes using uptake projections from discrete choice experiments (DCE) to better parameterize uptake and substitution in cost-effectiveness models. A simple impact model is developed and illustrated using an example from the HIV prevention field in South Africa. Comparison between the conventional approach and the DCE-based approach shows that, in our example, DCE-based impact predictions varied by up to 50% from conventional estimates and provided far more nuanced projections. In the absence of observed uptake data and to model the effect of variations in intervention characteristics, DCE-based uptake predictions are likely to greatly improve models parameterizing uptake solely based on expert opinion. This is particularly important for global and national level decision making around introducing new and probably more expensive interventions, particularly where resources are most constrained.

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KEY WORDS: discrete choice experiments; uptake; economic evaluation; low-income and middle-income country; user preferences; mathematical modelling

1. INTRODUCTION

In the early stages of introducing new health interventions such as novel products or services, there is often considerable uncertainty around their potential uptake, impact and cost-effectiveness. In such cases, mathematical modelling studies are frequently used to decide whether these new interventions could be cost-effective, with the results of these analyses critical for ultimately deciding whether or not to introduce the intervention. As such, it is crucial that models make realistic assumptions about levels of intervention uptake and how new interventions might affect the use of existing services or products. Before data on real-life uptake become available, models generally rely on trial data, expert opinion, observed uptake of comparable interventions, or model a range of uptake scenarios. Such uptake measures are likely to be highly uncertain and fail to account for the dynamic and heterogeneous manner in which individuals make decisions, for example, how users value a new product's characteristics differently such as reduction in risk (efficacy) or price and how this affects uptake and substitution from similar services or products. Even real-life uptake data will be highly context-specific and intervention-specific, and will not be useful for understanding how uptake could vary if the intervention was delivered differently.

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Experiments

The conventional modelling approach assumes uptake is uniform, that is, the same proportion of potential users will take up an intervention regardless of its characteristics such as efficacy or cost, and often apply a number of uptake assumptions. This assumption is currently the norm for economic evaluations in the HIV prevention field, with a given level of uptake assumed based on at best expert opinion or comparable products or services, but normally just assumed with no data to back up the assumption (Cremin *et al.*, 2013; Dimitrov *et al.*, 2011; Gomez *et al.*, 2012; Gray *et al.*, 2011; Terris-Prestholt *et al.*, 2014; Verguet *et al.*, 2013; Verguet and Walsh, 2010; Walensky *et al.*, 2012; Williams *et al.*, 2011).

Cost-benefit analyses can incorporate user preferences to value non-market impacts (Fujiwara and Campbell, 2011); however, the use of stated preference methods to explore the dynamic effect of intervention characteristics on uptake, and therefore intervention impact and cost-effectiveness, is novel. This letter illustrates the benefit of integrating user preferences into impact and cost-effectiveness models using an example from the HIV prevention field, where modelling is often used to inform decisions for health policy both at global and national levels. We propose the use of empirically collected preference data such as those generated through discrete choice experiments (DCEs). In DCEs, potential users make repeated choices between intervention scenarios. Varying the characteristics of these scenarios allows for explicit estimation of the magnitude of their effect on uptake. Importantly, DCEs generate data on how users may substitute to using new products or services away from existing behaviour, a critical model parameter.

The new approach allows the modelling of synergies among intervention attributes and both uptake and substitution between new and existing interventions. This letter proceeds as follows: Section 2 describes our theoretical model, and Section 3 uses the model to illustrate how DCE-based uptake projections can affect the modelled impact of introducing new HIV prevention technologies in South Africa. The discussion in Section 4 seeks to draw out the key implications of our letter. Box 1 provides an overview of terminology used.

Box 1: Definition of Terms

Efficacy:	The extent to which an intervention produces a benefit under ideal circumstances
Uptake:	The extent to which potential users adopts a new intervention
Adherence:	The extent to which a user, who has adopted an intervention, complies with a given regime as prescribed by the intervention
Use:	A function of uptake and adherence. The extent to which individuals sufficiently abide by an intervention's requisite behaviours
Effectiveness:	A function of efficacy, uptake and use. The extent to which an intervention produces a benefit under 'real-world' circumstances. Includes non-uptake and improper use.
Uniform Uptake:	The same proportion of potential users will uptake an intervention regardless of intervention characteristics such as efficacy or cost.

2. THEORETICAL MODEL

To demonstrate this approach, we compare the impact prediction of the conventional method, where uptake is assumed to be independent of intervention characteristics (i.e. uniform uptake) with those of a model using uptake and substitution predictions from DCE data. We use a simple model to estimate the short-term impact of two HIV prevention products on the average level of protection that an individual has. For a single product x , we assume the average protection against HIV, P_x , from product, x , is a function of its efficacy, E_x , and uptake (or use), U_x ,

$$P_x = E_x U_x \quad (1)$$

A second concern when introducing new products is that substitution may occur between effective (and likely cheaper) existing options and new potentially less effective or more expensive options. In the context of introducing a new prevention product, y , we assume that a proportion, U_{xy} , of those using existing product

x substitute for the new product y and a proportion U_{0y} of those not using any product start using product y . If the efficacy of the new product is E_y , then the total protection provided, P_{xy} , by the new (y) and existing (x) products is as follows:

$$P_{xy} = E_x U_x (1 - U_{xy}) + E_y (U_x U_{xy} + (1 - U_x) U_{0y}) \quad (2)$$

The additional protection provided by introducing the new product ($P_{xy} - P_x$) will depend on the efficacy of the new product and how the uptake and substitution away from existing products are related to this efficacy. In the following section, we illustrate this numerically in terms of HIV prevention impact, then consider the relevance for economic evaluations in LMIC.

3. AN EXAMPLE

This letter aims to illustrate the value of incorporating DCE-based uptake predictions into economic evaluations using an example from the HIV prevention field: the introduction of topical pre-exposure prophylaxis (TPPrEP) in South Africa. Also known as microbicides, TPPrEP is a relatively new HIV prevention technology. A recent trial showed TPPrEP could be effective for reducing the risk of HIV acquisition among HIV-negative women (Karim *et al.*, 2010) but with wide confidence intervals, estimating a per sex-act efficacy of 54%, ranging from 8 to 83% (Terris-Prestholt *et al.*, 2014). Note that this is less than the efficacy of condoms, and so substitution from condoms to TPPrEP could result in increased HIV transmission. We use the model in Equation 2 to compare the projected additional HIV protection provided by TPPrEP using conventional uptake assumptions with DCE-based uptake estimates from South Africa (Terris-Prestholt *et al.*, 2013). A household survey of 1017 adult women collected data on women's preferences for HIV prevention products including the male condom and TPPrEP. It measured women's preferences for product characteristics including HIV and pregnancy prevention efficacy (see Box 2 for more detail).

Box 2: Details of the DCE study underlying this analysis—Terris-Prestholt *et al.*, 2013

Data & Methods: A DCE was conducted via a random household survey among 1017 women in urban Gauteng Province, South Africa. Women were presented with choices between potential women's NPTs (microbicides, diaphragm, female condom) and 'what I did last time' (use or not use a condom) with different HIV and pregnancy prevention effectiveness and prices. Choice probabilities were estimated using the nested logit model and used to predict uptake.

Results: In this high HIV prevalence setting, HIV prevention effectiveness is the main driver of uptake followed by pregnancy prevention effectiveness. For example, a microbicide with poor effectiveness would have niche appeal at just 11% predicted uptake, while a highly effective microbicide (95% effective against HIV and pregnancy) would have far wider appeal (56% predicted uptake). Although women who reported not using condoms were more likely to choose the NPTs, at current very high rates of male condom use in South Africa (60%), about half of microbicide uptake is projected to be among those currently not using condoms.

Conclusions: Women are very interested in new HIV prevention technologies, especially if highly effective in preventing HIV and pregnancy. Women in greatest need were also most likely to switch to the new products.

As shown in Figure 1, predicted uptake of TPPrEP increased with its assumed efficacy and was greater among women who had not used condoms at their last sex-act (non-condom users) compared with those who had used a condom (condom users) (Terris-Prestholt *et al.*, 2013). For example, if TPPrEP is only 55% efficacious then the DCE predicts 11% of condom users will use the product, whereas 16% of non-condom users will use the product. However, if TPPrEP is 95% efficacious, then predicted uptake increases to 30% among condom users and 41% among non-condom users. Thus, using individual preference data

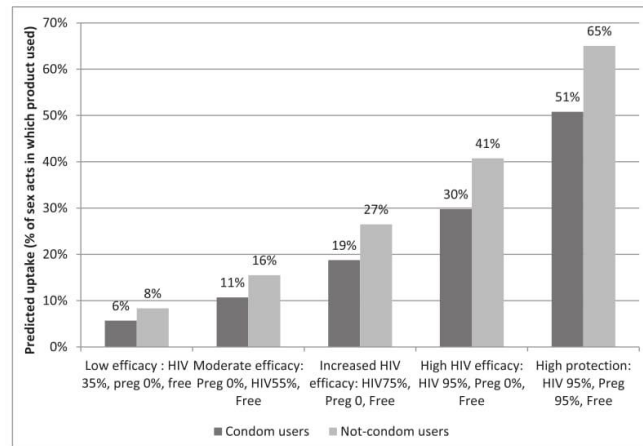


Figure 1. Predicted uptake of TPrEP by assumed HIV efficacy among condom and not-condom users (adapted from Terris-Prestholt *et al.*, 2013)

permits prediction of overall uptake and substitution between new and existing HIV prevention products by user and product characteristics. The method can further be refined to include additional intervention and user characteristics.

Using these uptake projections, we are able to model the incremental impact of introducing TPrEP into a population of adult women in Gauteng, South Africa, where the DCE data were collected. We start with the

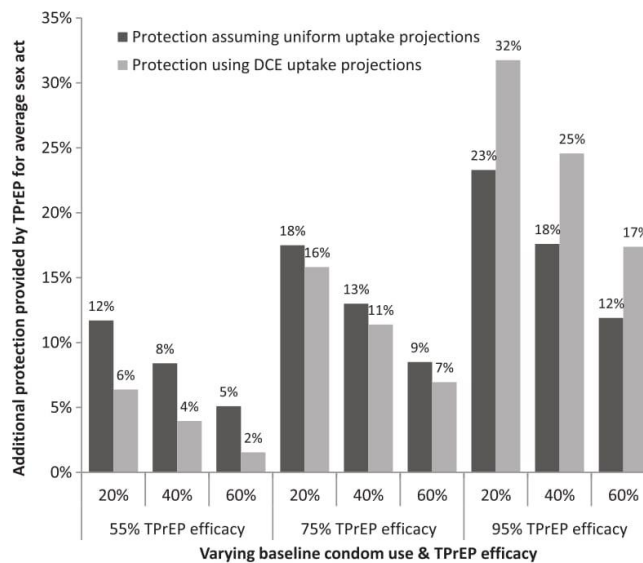


Figure 2. Comparison of additional HIV protection estimated using conventional uniform uptake assumptions and the DCE-based uptake predictions: variation by baseline condom use and the efficacy of TPrEP

estimated average protection provided by condoms at different levels of use applying Equation (1). We introduce these predictions into the simple theoretical model of HIV protection in Equation (2) and estimate the incremental impact as $P_{xy} - P_x$. Assuming condoms are 85% effective (Pinkerton and Abramson, 1997; Pinkerton *et al.*, 1998) then at 20% condom use, the average per sex-act protection is 18% before TPrEP introduction and 51% at 60% condom use.

Figure 2 presents the estimates of the incremental HIV protection provided from adding TPrEP into the method mix in two ways: firstly using uniform uptake predictions (the left bar in each pair) and secondly, using uptake and substitution parameters from the DCE (right bar in each pair). The uniform uptake assumption based on expert opinion assumes that 30% of non-condom users would use TPrEP and 5% of condoms users would switch to TPrEP, regardless of TPrEP efficacy (Terris-Prestholt *et al.*, 2014).

By allowing for variation in uptake according to TPrEP efficacy, the model predicts that introducing 55% efficacious TPrEP into a population with 20% condom use results in 6% additional population protection compared with when just condoms were used—half the impact predicted (12%) with the uniform uptake assumption. However, when a 95% efficacious TPrEP is considered, higher uptake is predicted than from expert opinion, resulting in 32% additional population protection, nearly 50% more than was predicted (23%) with the uniform uptake assumption. The difference between the TPrEP impact projections for the uniform and DCE uptake predictions is smaller at 75% efficacy but is similar across different levels of baseline condom use.

4. DISCUSSION

To inform model based cost-effectiveness analyses, this study proposes the use of DCEs to estimate the likely uptake of new products as well as substitution away from existing products. It illustrates how economic evaluation estimates that rely on modelled impact projections could be severely biased, off by up to 50% in our example, if simple uptake assumptions are applied that fail to account for the synergistic relationship between uptake and substitution and the intervention characteristics. DCEs provide one approach to estimating uptake that can inform modelling in the absence of observed uptake data.

An important assumption of our proposed method is that DCEs (and other stated preference approaches) have sufficient external validity to accurately predict real-world behaviour. A number of studies in the health literature have compared stated-preference measures with participants' actual behaviour, or revealed preferences (Lancsar and Swait, 2014). Generally, these have found that stated-preference techniques are strongly associated with the direction in which people value different products (Ryan and Watson, 2009) and are often not significantly different from revealed preference estimates of magnitude (Mark and Swait, 2004; Kesternich *et al.*, 2013). However, more research is needed to better understand how well DCEs predict not only uptake and failure to take up new health interventions as well as how to design and analyse DCEs to strengthen their external validity. Lancsar and Swait (2014) recently proposed key study designs to evaluate external validity of DCEs, providing a framework upon which to build future validation studies. Early exploratory work is starting to emerge providing more nuanced evidence on their external validity: for example, the positive predictive value may be far better than the negative predictive value (Lambooij *et al.*, 2015; Salampessy *et al.*, 2015), and aggregated uptake predictions are likely to obscure individual level variability in preference (Krucien *et al.*, 2014). The use of labelled DCEs, where alternatives are named explicitly (for example 'male condom', 'TPrEP' rather than 'Alternative A', 'Alternative B') has been shown to increase external validity (De Bekker-Grob *et al.*, 2010), as has carrying out experiments in populations with experience of making decisions relevant to the experiment's context (Groom *et al.*, 2004; Blomquist and Whitehead, 1998). In this case, condom users have already made a proactive and informed decision to use HIV and pregnancy protection, perhaps making their indications of substitution to a less effective new product more reliable.

Stated preference methods such as DCEs are used to explore preferences at a single time point (i.e. whether or not an individual changes his or her behaviour), and are not generally predictive of time-variant or long-term, repeated activities. Many interventions require long-term adherence to produce a substantial effect, but stated preference methods are generally unable to describe if, and how much, individuals will adhere to an intervention. However, initial uptake is a necessary, albeit insufficient, condition for long-term impact.

The introduction of a new single-purpose technology such as TPrEP has given rise to concerns that people will stop using existing multi-purpose technologies such as condoms, decreasing pregnancy protection as well as protection for other sexually transmitted infections (STIs) (Karim *et al.*, 2010; Underhill, 2013). Data from DCEs allow us to interrogate the degree to which people may switch methods. Expert opinion suggested that around 5% of people would swap condoms for TPrEP, irrespective of efficacy, whereas the DCE data suggest a more nuanced view with the degree of substitution being dependent on intervention efficacy. For instance, the data predict that 11% of condom users would switch to a 55% efficacious TPrEP but up to 30% for a 95% efficacious TPrEP. This is important because substitution may have effects on wider STI disease burden and ultimately temper the additional benefit new technologies could provide, worsening their overall cost-effectiveness. Within the HIV prevention field, this analysis could be expanded to show how synergies with other product characteristics can be modelled explicitly such as how uptake and substitution may change with the cost of the product or with the addition of protection against pregnancy or other STIs.

User preferences can also be used to model the potential impact and cost-effectiveness of other interventions where uptake or use of an intervention is driven by its characteristics, and/or observational data are not yet available, such as stimulating demand for treated bed nets to prevent malaria, malaria vaccinations and voluntary medical male circumcision (Aigbogun *et al.*, 2015; Desrochers *et al.*, 2014; Thirumurthy *et al.*, 2014). Consideration of consumer preferences for different characteristics of these interventions, such as efficacy or aesthetic appeal, may better inform modelling their potential cost-effectiveness and optimal design of demand-creation strategies.

At present, infectious disease models tend to use probabilistic sensitivity analysis (PSA) to account for uncertainty in model predictions. However, PSAs do not commonly consider the interdependence of uptake, efficacy and substitution parameters. It is possible that PSA could consider these relationships, but without data to parameterize these relationships, the considerable uncertainty this method would incorporate into the model estimates could reduce their usefulness. The method proposed in this letter could indeed be used in conjunction with PSA: DCE data could be used to parameterize a PSA, giving distributional information for the parameters and the interactions between these factors to ultimately reduce uncertainty in the model and its PSA.

As quantitative data on drivers of uptake are rare for new interventions, this study proposes the use of DCE data to strengthen economic evaluations. We suggest that assuming uniform uptake in economic evaluations could erroneously support or reject the adoption of a new technology. This is of particular concern in low-income and middle-income settings due to considerable strains on healthcare and research spending, alongside an often high burden of ill health.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ETHICS STATEMENT

This letter uses only secondary data publically available in the literature, and no specific ethical approval was required.

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Appendix IV: Letters from ethics committees

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10005, 10th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: PV Tobias Building Room 306, 3rd Floor. Tel +27 (0)11-717-2700
Private Bag 3, Wits 2050, www.wits.ac.za. Fax +27 (0)11-717-1265

10 September 2015

Maria Cabrera

Wits Reproductive Health and HIV Institute
Hillbrow Health Precinct
22 Esselen Street
Hillbrow
Johannesburg
2001

Sent by email to: mcabrera@wrhi.ac.za

Dear Ms Cabrera

Re: Protocol Ref no: M140614

Protocol Title: Preferences for ARV Based Prevention in Gauteng, South Africa

Principal Investigator: Prof Sinead Delany-Moretlwe

Protocol Amendment

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has approved the following amendments on the above mentioned study, as detailed in your letter dated 11 August 2015.

- Protocol version 2.0 dated August 2015
- Information Sheet and Consent Form (Focus Group Discussions) version 2.0 dated August 2015
 - Adults
 - Parent/Legal Guardian
 - Assent (FGD and Survey)

Thank you for keeping us informed and updated.

Yours Sincerely,

.....
Ms Zanele Ndlovu

Administrative Officer

Human Research Ethics Committee (Medical)



London School of Hygiene & Tropical Medicine

Keppel Street, London WC1E 7HT

United Kingdom

Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk**LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE****Observational / Interventions Research Ethics Committee**

Dr Fern Terris-Prestholt

Lecturer in economics of HIV

Department of Global Health and Development (GHD) / Public Health and Policy (PHP)

LSHTM

13 October 2015

Dear Dr Terris-Prestholt,

Study Title: Preferences for ARV based prevention in Gauteng, South Africa**LSHTM Ethics Ref:** '8451- 2'

Thank you for your letter responding to the Observational Committee's request for further information on the above amendment to research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above amendment to research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval for the amendment having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Other	1. Survey tool and Discrete Choice Experiments V2.0 (30.9.2015) markup	09/10/2015	2
Other	2. Informed Consent Forms V1.1 (30.9.2015) markup	09/10/2015	1.1
Other	HREC Approval (1)	09/10/2015	1
Other	HREC survey and consent form revisions approval	09/10/2015	1
Covering Letter	12 October 2015-response	12/10/2015	1
Other	SOP for Handling Sensitive Issues v1.1 clean	13/10/2015	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: <http://leo.lshtm.ac.uk>Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

**Professor John DH Porter**
Chairethics@lshtm.ac.uk<http://www.lshtm.ac.uk/ethics/>

Appendix V: NGENE output for 10- and 15-task DCEs

15-task DCE:

MNL efficiency measures															
D error	0.573407														
A error	1.264644														
B estimate	26.03064														
S estimate	63.416701														
Prior	product(e0)	product(e1)	product(e2)	product(e3)	hiv(e0)	hiv(e1)	preg(e0)	freq(e0)	freq(e1)	freq(e2)	freq(e3)	freq(e4)	freq(e5)	sti(e0)	sideef
Fixed prior value	0.41362	1.51871	1.21778	0.14186	1.76106	0.50759	-0.65266	-1.32439	-1.57733	-0.87182	-0.92217	-0.79877	-0.22058	-0.6385	0.200
Sp estimates	32.306089	4.078636	3.451617	63.416701	2.562122	5.488404	3.345217	4.530136	5.174437	9.565926	7.88617	8.976367	63.223148	4.795237	47.27
Sp t-ratios	0.344837	0.970507	1.054981	0.246124	1.224493	0.836629	1.071628	0.920875	0.861637	0.633713	0.697948	0.654193	0.246501	0.895058	0.285
Design															
Choice situation	a.product	a.hiv	a.preg	a.freq	a.sti	a.sideeffs	b.product	b.hiv	b.preg	b.freq	b.sti	b.sideeffs	c.product	c.hiv	c.preg
1	2	55	1	3	1	1	2	75	0	1	0	3	1	55	0
2	1	55	0	6	1	3	1	95	1	5	1	2	3	95	1
3	1	95	0	4	0	2	2	55	1	5	1	0	1	55	0
4	3	75	0	5	0	3	5	55	0	6	0	1	2	55	1
5	2	55	0	2	1	2	2	55	0	2	0	0	3	95	0
6	3	95	0	2	0	2	4	95	0	0	1	0	5	95	1
7	4	95	0	5	0	1	3	75	0	1	0	3	2	75	0
8	3	55	1	3	1	1	3	55	1	4	1	0	5	75	1
9	5	95	1	0	0	0	5	55	1	6	1	2	4	75	1
10	4	75	1	4	0	1	1	75	1	2	0	2	5	95	1
11	5	95	0	1	0	0	4	95	1	0	0	3	3	75	0
12	5	75	1	6	0	0	5	95	0	3	0	1	4	55	0
13	4	75	1	0	1	2	3	75	0	0	0	1	2	75	0
14	2	75	1	0	1	3	1	95	0	4	1	1	4	55	0
15	1	55	0	1	1	0	4	75	1	3	1	2	1	95	1

10-task DCE:

MNL efficiency measures														
D error	1.083647													
A error	2.561759													
B estimate	37.370101													
S estimate	134.216005													
Prior	product(e0)	product(e1)	product(e2)	product(e3)	hiv(e0)	hiv(e1)	preg(e0)	freq(e0)	freq(e1)	freq(e2)	freq(e3)	freq(e4)	freq(e5)	sti(e0)
Fixed prior value	0.41362	1.51871	1.21778	0.14186	1.76106	0.50759	-0.65266	-1.32439	-1.57733	-0.87182	-0.92217	-0.79877	-0.22058	-0.6385
Sp estimates	40.884714	7.882537	6.832781	134.160076	4.108196	15.647515	7.584431	6.003482	6.662115	18.029511	27.711232	31.654065	134.216005	11.62513
Sp t-ratios	0.306532	0.698109	0.749821	0.169217	0.967009	0.495488	0.711696	0.799935	0.759364	0.461598	0.37233	0.34837	0.169182	0.574853
Design														
Choice situation	a.product	a.hiv	a.preg	a.freq	a.sti	a.sideeffs	b.product	b.hiv	b.preg	b.freq	b.sti	b.sideeffs	c.product	c.hiv
1	1	55	1	4	1	1	1	55	1	5	1	0	2	55
2	1	95	0	1	1	2	5	75	0	6	0	3	4	95
3	5	95	1	0	1	1	4	95	1	4	0	3	3	75
4	4	75	0	6	0	0	2	95	1	2	1	1	1	75
5	3	95	0	2	0	2	1	95	0	1	0	1	5	95
6	5	95	1	3	0	0	3	55	1	2	1	0	4	75
7	2	75	0	1	0	0	4	75	1	1	1	2	1	95
8	2	55	1	0	1	3	5	95	0	0	0	1	2	55
9	3	75	0	5	0	3	2	55	0	3	1	0	5	95
10	4	55	1	2	1	1	3	75	0	0	0	2	3	55

Appendix VI: Information sheets and informed consent forms

Informed consent form and information sheet: Survey - Adults

Hello, my name is I am working for Progressus Research and Development on a project for the Wits Reproductive Health and HIV Institute and the London School of Hygiene and Tropical Medicine. I would like to invite you to participate in a research study with people from Ekurhuleni.

Why are we conducting this study?

Many people in South Africa are infected with HIV every day. Often it is because people find it difficult to persuade their partners to use condoms. At the moment, the male and female condoms are the only widely available methods of preventing HIV. Researchers are currently developing new methods that people can use such as daily tablets, topical microbicides, long-acting injectable anti-retrovirals, diaphragms with microbicides and intra-vaginal rings.

What is this study about?

This study aims to understand the reason that people may decide to use these newer methods, if they are found to be effective. We are interested in what people think about these new methods and what features are important to increase uptake and ensure continued use. We are also interested in how couples choose prevention methods together. This study will provide us with important information necessary to develop new prevention methods for men and women to use against HIV.

REMEMBER: WE ARE NOT PROVIDING ANY PRODUCTS FOR THIS STUDY

Who can take part?

You can take part if you:

- Are willing to answer survey questions
- Are between the age of 18 and 45
- Have had sexual intercourse at least once in the past 6 months

What do you have to do if you agree to take part?

Respond to survey questions.

You have been asked to respond to survey questions. The survey will take approximately 45 minutes of your time.

All questionnaires will be kept securely on a computer server. No one except program staff will be able to view the material. This information will be used by us to gain more insights into what sorts of HIV prevention methods men and women would prefer.

Will the study benefit you?

There is no immediate benefit to you by participating in this part of the study. However, you will be given a phone card worth R50 as token of thanks for your participation.

What are the risks?

The interview may ask some personal questions about your relationships, your sex life and your HIV status. If these interviews raise any concerns for you, we will refer you to medical assistance. We would like to reassure that these interviews are confidential and the information that you share with us will not be shared with others.

Will the information from this survey be confidential?

Yes, all results of the survey will be confidential. You will not be identified by name on any documentation. No one will have access to your information other than the researchers and this will be stored on a password restricted computer server.

What happens if you change your mind about taking part?

You can withdraw from the interview at any time without giving a reason. Withdrawal from the interview will not negatively affect you or your access to care.

What happens if I have any problems during the individual interview?

If you have a problem resulting from your participation in this interview, please contact the investigators: Maria Cabrera or Robyn Eakle or Prof Sinead Delany-Moretlwe at Wits RHI in South Africa **on Tel: 011 358 5100**, or Fern Terris-Prestholt in London; **on Tel: +44207927 2271**.

This study has been approved by the Human Research Ethics Committee (Medical) Contact details: Prof P Cleaton-Jones, HREC (Medical) Chairperson, Tel 011 717 2302, peter.cleaton-jones@wits.ac.za. Secretariat: Ms Z Ndlovu, Tel 717 1252, Zanele.ndlovu@wits.ac.za, Ms A Keshav, Tel 011 717 2700, anisa.keshav@wits.ac.za

We will refer you for appropriate medical help if needed.

STATEMENT OF INFORMED CONSENT

The participant must complete the following questions herself/with a staff member who did not administer the consent		
Have you had an opportunity to read the consent form/have it read to you?	YES	NO
Have you had an opportunity to ask questions and discuss this study?	YES	NO
Have you received satisfactory answers to all of your questions?	YES	NO
Have you received enough information about the study?	YES	NO
Do you understand the benefits of the study?	YES	NO
Do you understand the risks of the study?	YES	NO
Which study staff member have you spoken to about the study? PLEASE PRINT HIS/HER NAME: _____		
Do you understand that you are free to withdraw from the interview at any time without having to give a reason for withdrawing?	YES	NO

Do you agree to take part in this study?	YES	NO
If the participant answers NO to any of the above questions then she may not be enrolled in the study.		
Printed name of Investigator (the interviewer)		Date
Signature on behalf of participant		Time

Informed consent form and information sheet: Parents/guardians of adolescent girls

Hello, my name is I am working on for Progressus Research and Development on a project for the Wits Reproductive Health and HIV Institute and the London School of Hygiene and Tropical Medicine. I would like to invite you to participate in a research study with young women from Ekurhuleni.

Why are we conducting this study?

Many people in South Africa are infected with HIV every day. Often it is because people find it difficult to persuade their partners to use condoms. At the moment, the male and female condoms are the only widely available methods of preventing HIV. Researchers are currently developing new methods that people can use such as daily tablets, topical microbicides, long-acting injectable anti-retrovirals, diaphragms with microbicides and intra-vaginal rings.

What is this study about?

This study aims to understand the reason that people may decide to use these newer methods, if they are found to be effective. We are interested in what people think about these new methods and what features are important to increase uptake and ensure continued use. We are also interested in how couples choose prevention methods together. This study will provide us with important information necessary to develop new prevention methods for men and women to use against HIV.

REMEMBER: WE ARE NOT PROVIDING ANY PRODUCTS FOR THIS STUDY

Who can take part?

Because your daughter/ward is below 18 years old, you will need to give permission for the young person in your care to be in this study. Your decision and her decision to join the study is voluntary—that means it is up to you. You may refuse to allow her to join, or you may withdraw her from the study, for any reason and at any time. If the young person decides she does not want to consent to participate in the study, even if you have already given consent for her, the young person will not be enrolled in the study.

An adolescent girl can take part if:

- She is between the age of 16-17 years
- She is willing to participate in an individual interview
- You have given consent for her to take part.

What does your daughter/ward have to do if you and her agree for her to take part?

Respond to survey questions.

Your ward has been asked to participate in a survey which is completed on a tablet computer. This will take approximately 45 minutes of her time.

All questionnaires will be kept securely on a computer server. No one except program staff will be able to view the material. This information will be used by us to gain more insights into what sorts of HIV prevention methods men and women would prefer. By allowing your daughter/ward to participate you are helping us decide on how to do research on new prevention technologies.

Will the study benefit you?

There is no immediate benefit to you or your ward by participating in this part of the study. However, she will be given a phone card worth R50 as token of thanks for her participation.

What are the risks?

The interview may ask some personal questions about your daughter or ward. If these interviews raise any concerns, we will refer her for medical assistance. We would like to reassure you that these interviews are confidential and the information that she shares with us will not be shared with others

Will the information from these interviews be confidential?

Yes, all results of the survey will be confidential. We ask that you provide a private space for us to interview your daughter/ward. Alternatively, we will invite her to a private venue so that we can conduct the interview with her. Her responses will be private and confidential and you will not have access to them. Your child/ward will not be identified by name on any documentation. No one will have access to your or her information other than the researchers and this will be stored on a password restricted computer server.

What happens if you change your mind about her taking part?

You can withdraw your ward from the interview at any time without giving a reason. Withdrawal from the interview will not negatively affect your ward or her access to care.

What happens if I have any problems during the survey?

If you have a problem resulting from your participation in this interview, please contact the investigators: Maria Cabrera or Robyn Eakle or Prof Sinead Delany-Moretlwe at Wits RHI in South Africa **on Tel: 011 358 5100**, or Fern Terris-Prestholt in London; **on Tel: +44207927 2271**.

This study has been approved by the Human Research Ethics Committee (Medical) Contact details: Prof P Cleaton-Jones, HREC (Medical) Chairperson, Tel 011 717 2302, peter.cleaton-jones@wits.ac.za. Secretariat: Ms Z Ndlovu, Tel 717 1252, Zanele.ndlovu@wits.ac.za, Ms A Keshav, Tel 011 717 2700, anisa.keshav@wits.ac.za

We will refer your daughter or ward for appropriate medical help if needed.

STATEMENT OF INFORMED CONSENT

The participant must complete the following questions herself/with a staff member who did not administer the consent		
Have you had an opportunity to read the consent form/have it read to you?	YES	NO
Have you had an opportunity to ask questions and discuss this study?	YES	NO
Have you received satisfactory answers to all of your questions?	YES	NO
Have you received enough information about the study?	YES	NO

Do you understand the benefits of the study?	YES	NO
Do you understand the risks of the study?	YES	NO
Which study staff member have you spoken to about the study? PLEASE PRINT HIS/HER NAME: _____		
Do you understand that you are free to withdraw from the interview at any time without having to give a reason for withdrawing?	YES	NO
Do you agree to take part in this study?	YES	NO
If the participant answers NO to any of the above questions then she may not be enrolled in the study.		
Printed name of Investigator (the interviewer)		Date
Signature on behalf of participant		Time

Informed assent form and information sheet: Survey – Adolescent Girl

Hello, my name is I am working for Progressus Research and Development on a project for the Wits Reproductive Health and HIV Institute and the London School of Hygiene and Tropical Medicine. I would like to invite you to participate in a research study on young women from Ekurhuleni.

Why are we conducting this study?

Many adolescent girls in South Africa are infected with HIV every day. Often it is because young women find it difficult to persuade their partners to use condoms. At the moment, the male and female condoms are the only widely available methods of preventing HIV. Researchers are currently developing new methods that people can use such as daily tablets, topical gels, long-acting injectable anti-retrovirals, diaphragms to be used with or without gels and intra-vaginal rings.

What is this study about?

This study aims to understand the reason that people may decide to use these newer methods, if they are found to be effective. We are interested in what people think about these new methods and what features are important to increase uptake and ensure continued use. We are also interested in how couples choose prevention methods together. This study will provide us with important information necessary to develop new prevention methods for men and women to use against HIV.

REMEMBER: WE ARE NOT PROVIDING ANY PRODUCTS FOR THIS STUDY

Who can take part?

You can take part if you:

- Are willing to answer survey questions
- Are between the age of 16 and 17 years
- Your parent/guardian consents for you to participate

What do you have to do if you agree to take part?

Respond to survey questions.

You have been asked to respond to survey questions. The survey will take approximately 45 minutes of your time.

All questionnaires will be kept securely on a computer server. No one except program staff will be able to view the material. This information will be used by us to gain more insights into what sorts of HIV prevention methods men and women would prefer.

Will the study benefit you?

There is no immediate benefit to you by participating in this part of the study. However, you will be given a phone card worth R50 as token of thanks for your participation.

What are the risks?

The interview may ask you some personal questions. If these interviews raise any concerns for you, we will refer you to medical assistance. We would like to reassure that these

interviews are confidential and the information that you share with us will not be shared with others.

Will the information from this survey be confidential?

Yes, all results of the survey will be confidential. You will not be identified by name on any documentation. No one will have access to your information other than the researchers and this will be stored on a password restricted computer server.

What happens if you change your mind about taking part?

You can withdraw from the interview at any time without giving a reason. Withdrawal from the interview will not negatively affect you or your access to care.

What happens if I have any problems during the individual interview?

If you have a problem resulting from your participation in this focus group discussion, please contact the investigators: Maria Cabrera or Robyn Eakle or Prof Sinead Delany-Moretlwe at Wits RHI in South Africa **on Tel: 011 358 5100**, or Fern Terris-Prestholt in London; **on Tel: +44207927 2271**.

This study has been approved by the Human Research Ethics Committee (Medical) Contact details: Prof P Cleaton-Jones, HREC (Medical) Chairperson, Tel 011 717 2302, peter.cleaton-jones@wits.ac.za. Secretariat: Ms Z Ndlovu, Tel 717 1252, Zanele.ndlovu@wits.ac.za, Ms A Keshav, Tel 011 717 2700, anisa.keshav@wits.ac.za

We will refer you for appropriate medical help if needed.

STATEMENT OF INFORMED CONSENT

The participant must complete the following questions herself/with a staff member who did not administer the consent		
Have you had an opportunity to read the consent form/have it read to you?	YES	NO
Have you had an opportunity to ask questions and discuss this study?	YES	NO
Have you received satisfactory answers to all of your questions?	YES	NO
Have you received enough information about the study?	YES	NO
Do you understand the benefits of the study?	YES	NO
Do you understand the risks of the study?	YES	NO
Which study staff member have you spoken to about the study? PLEASE PRINT HIS/HER NAME: _____		
Do you understand that you are free to withdraw from the interview	YES	NO

at any time without having to give a reason for withdrawing?			
Do you agree to take part in this study?		YES	NO
If the participant answers NO to any of the above questions then she may not be enrolled in the study.			
Printed name of Investigator (the interviewer)		Date	
Signature on behalf of participant		Time	

Informed Consent Form and Information Sheet: Focus Group Discussions

Hello, my name is I am working for Progressus Research and Development on a project for the Wits Reproductive Health and HIV Institute and the London School of Hygiene and Tropical Medicine. I would like to invite you to participate in a research study on women, men and adolescent girls from Ekurhuleni.

Why are we conducting this study?

Many people in South Africa are infected with HIV every day. Often it is because people find it difficult to persuade their partners to use condoms. At the moment, the male and female condoms are the only widely available methods of preventing HIV. Researchers are currently developing new methods that people can use to prevent HIV such as daily tablets, topical gels, long-acting injectable anti-retrovirals, diaphragms to be used with or without gels and intra-vaginal rings.

What is this study about?

This study aims to understand the reason that people may decide to use these newer methods for HIV prevention, if they are found to be effective. We are interested in what people think about these new methods and what features are important to increase uptake and ensure continued use. We are also interested in how couples choose prevention methods together. This study will provide us with important information necessary to develop new prevention methods for men and women to use against HIV.

REMEMBER: WE ARE NOT PROVIDING ANY PRODUCTS FOR THIS STUDY

Who can take part?

You can take part if you:

- Are willing to participate in a focus group discussion
- Are between the age of 18 and 45
- Have had sexual intercourse at least once in the past 6 months

What do you have to do if you agree to take part?

You have been asked to participate in focus group discussions. The focus group discussion will take approximately two hours of your time.

All focus group discussions will be recorded on audio tape. This is to ensure that the information we collect is accurately recorded. Later we will write down the information and store this on a computer. All digital recorders will be kept in a locked cabinet. No one except program staff will be able to listen to the digital recorder or view the material. After the research has been completed all audio tape recordings will be destroyed.

This information will be used by us to gain more insights into how to ask people what features of the new prevention methods are most important and how they would choose between them. By participating you are helping us decide on how to do research on new prevention technologies.

Will the information from these focus group discussions be confidential?

As researchers we will ensure that you will not be identified by name on any documentation. No one will have access to any recordings and all digitally recorded voice files will be destroyed at the end of the study. We cannot, however, guarantee that other participants in the focus group discussion maintain your confidentiality but will encourage confidentiality through a discussion of this issue with all participants before the FGD starts. We will attempt to ensure that all participants maintain one another's confidentiality by requesting that you, or any of the participants, do not discuss the content of what any of the participants said during the focus group discussion with any people outside. This is to ensure your opinion and other people's opinions and experiences are kept confidential. But you should carefully consider the information that you choose to share with the group as we cannot guarantee that other participants will maintain confidentiality

Will the study benefit you?

There is no immediate benefit to you by participating in this part of the study. However, you will be offered a phone airtime voucher to the value of R50.00 as a token of appreciation.

What are the risks?

The focus group discussions may discuss some personal issues. You will also be asked to discuss your experiences in a group setting but you may choose not to tell what you consider private information in the company of others. Although all participants are requested to not discuss what has been said during these discussions with anyone else, we cannot guarantee full confidentiality.

What happens if you change your mind about taking part?

You can choose not to answer any of the questions that you do not want to answer. You can withdraw from the focus group discussion at any time without giving a reason. Not answering specific questions or withdrawal from the discussion will not negatively affect you.

What happens if I have any problems during the individual interview?

If you have a problem resulting from your participation in this focus group discussion, please contact the investigators: Maria Cabrera or Robyn Eakle or Prof Sinead Delany-Moretlwe at Wits RHI in South Africa **on Tel: 011 358 5100**, or Fern Terris-Prestholt in London; **on Tel: +44207927 2271**.

Who has approved this study?

This study was reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee (Medical). For more information or if you have any concerns or complaints please contact Prof P Cleaton-Jones, the HREC (Medical) Chairperson, (Tel 011 717 2302 or email: peter.cleaton-jones@wits.ac.za) or contact the secretariat: Ms Z Ndlovu, (Tel 717 1252 or email: Zanele.ndlovu@wits.ac.za) OR Ms A Keshav (Tel 011 717 2700 or email: anisa.keshav@wits.ac.za)

The participant must complete the following questions herself/with a staff member who did not administer the consent		
Have you had an opportunity to read the consent form/have it read to you?	YES	NO
Have you had an opportunity to ask questions and discuss this study?	YES	NO
Have you received satisfactory answers to all of your questions?	YES	NO
Have you received enough information about the study?	YES	NO
Do you understand the benefits of the study?	YES	NO
Do you understand the risks of the study?	YES	NO
Which study staff member have you spoken to about the study? PLEASE PRINT HIS/HER NAME: _____		
Do you understand that you are free to withdraw from the interview at any time without having to give a reason for withdrawing?	YES	NO
Do you agree to take part in this study?	YES	NO
If the participant answers NO to any of the above questions then she may not be enrolled in the study.		
Printed name of Investigator		Date
Signature of participant		Time

Consent for audio recording of interviews

Do you agree to the interview being audio recorded?	YES	NO
Printed name of Investigator		Date
Signature of participant		Time

Do you agree that some of your responses be quoted in a manner in which you cannot be identified?	YES	NO
Printed name of Investigator		Date
Signature of participant		Time

Appendix VII: Focus group discussion guide

Interviewer	<input type="text"/>	Date	<input type="text"/>
Venue	<input type="text"/>		

INSTRUCTIONS FOR THE MODERATOR – How to use this FGD Guide

1. There are 3 levels of questions:

- Numerical research questions/topic areas highlighted in grey: the questions/areas that we as researchers want to get answers to. These don't need to be read aloud.
- Discussion questions: the questions that you as the Interviewer will ask respondents in order to get answers to the research questions. **These questions will be underlined and in bold.**
- Probes: they are indicated with a bullet. The interviewer should ensure that key topics listed in the probes have been addressed/discussed during the interview. So, depending on what has already been discussed you may ask these probes or not.

2. *Instructions/suggestions to interviewer are in italics and brackets [].*

3. The discussion guide is divided into three columns.

- **The left-hand column** contains the research questions, discussion questions and probes. The discussion questions are suggestions for getting the discussion going. It is not required to read them verbatim, but they are written to ensure some consistency across discussion. You may adapt the question, depending on how the discussion develops, and you as the Interviewer will have to ensure that at the end the research questions have been answered.
- **The right-hand column** is for summarising the themes brought up by the women in the discussions. These should be summaries of the general issues raised in connection with the research question. These summaries should be more than just yes/no, but not longer than a few sentences of bullet points. They do not need to be detailed, as we have the details on the tape.

INTRODUCTION

Welcome the participants and thank them for coming. Hand each participant a sociodemographic information sheet.

Explain the general purpose of the discussion:

“We are holding a few discussions with up to 10 women at a time to talk about your experiences of negotiating with clients and other partners. We would like to find out your experiences when convincing men to use condoms, as well as how you agree an amount of money men give you for sex.”

Introduce the team and the different roles of the members.

Outline general ground rules such as the importance of everyone speaking up, talking one at a time, and being prepared for the moderator to interrupt to assure that all the topics can be covered.

Address the issue of confidentiality: Inform the group that information discussed is going to be analysed as a whole and that the participants' names will not be used in any analysis of the discussion.

Explain the presence and purpose of audio recording equipment.

Before starting the discussion, the Interviewer explains to the group (please state verbatim):

We will begin the tape recorder now. [Interviewer: *start the tape recorder.*]

As you know from your informed consent, this focus group discussion will be tape recorded today. Please verbally indicate that you are aware that we are tape recording this session and that it is okay with you. [Interviewer: *be sure to get a verbal okay from the group.*]

Have the group members introduce themselves. They should create a nickname for the discussion. Have them write it down on a sheet of paper that they will keep on their laps and refer to throughout the discussion.

Ask for any questions.

Ask “ice-breaker”: Go round the group and ask each participant to introduce themselves by their nickname and ask them to share the strangest or funniest thing that happened to them in the last week.

Today we are going to talk about different types of sexual partners. First, let's talk about clients. By clients I mean men who give you money in return for sex.

You may have clients you see just once or a few times, but you do not know them well. We will call these occasional clients. You may have clients you see more regularly, who you know and recognise well. We will call these regular clients.

Can you explain back to me your understanding of what these different types of clients are? It might help to think about what type of client you last had sex with?

	Research Question, Focus Group Questions and Probes	Summary/Notes
1.	<p>What types of client characteristics do sex-workers prefer?</p> <p><u>What makes a good client?</u></p> <ul style="list-style-type: none"> • Could you describe your ideal client? • Do you prefer clients who you see regularly, or those you see occasionally? Why? 	

2.	<p>What characteristics make it more or less likely that sex workers will insist on using a condom?</p> <p><u>What kind of clients do you think women should always use condoms with?</u></p> <ul style="list-style-type: none"> • What are these clients like? • What sort of protection would you use? Male condoms? Female condoms? • Does it make a difference if they are an occasional client? What about a regular client? • What about clients who look like they might have an infection? 	
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3.	<p>What are sex worker's perceptions on their negotiation power for protection?</p> <p><u>How do you get your clients to use condoms?</u></p> <ul style="list-style-type: none"> • Is it always possible to persuade clients to use a condom? • Is this different for regular or occasional clients? • What issues might people have trying to make clients use condoms? <p>Reminder: Client: a man who gives you money in return for sex</p> <p>Occasional Clients: clients you see just once or a few times, but you do not know them well.</p> <p>Regular Clients: clients you see more regularly, who you know and recognise well</p>	
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5.	<p>What makes it more or less likely that sex workers will insist on using a condom?</p> <p><u>When do you think women might not use a condom?</u></p> <ul style="list-style-type: none"> • What makes it more or less likely that women will use a condom? • Do you think the chance to earn more money influences women's decisions to use condoms? 	
----	--	--

6.	<p>How do sex-workers negotiate price with clients?</p> <p><u>How do you agree on the amount of money a client gives you for sex?</u></p> <ul style="list-style-type: none"> • Are there standard rates you charge for services, or does it depend on the situation? • What sorts of things make you reduce or increase the amount? • Do you suggest an amount, or do you wait for the client to offer an amount? 	
----	---	--

7.	<p>Does disclosure of FSW HIV status affect condom use and price with clients?</p> <p><u>What do you think about disclosing your HIV status to clients? Does it affect whether you use a condom?</u></p> <ul style="list-style-type: none"> • Would you disclose your status to a client? Why? • Have you done it before? What happened? • Would it affect the amount of money a client gives you? 	
----	--	--

Now let's talk about sexual partners who do not give you money in return for sex.

One type is a main partner, like a husband, boyfriend, or someone you might call an emotional partner that you see regularly whom you do not see as a client and who does not give you money or gifts in exchange for sex.

Another type is a casual partner, someone you might see from time to time but whom you do not consider to be someone you are in a serious relationship with and who is also not a client.

7.	<p>How do FSWs perceive risk from clients and regular partners?</p> <p><u>Do you think sex workers are more likely to get HIV from their paying clients or from their main partners, like a boyfriend or husband? Why?</u></p> <ul style="list-style-type: none"> • Are romantic/main partners more or less likely to use condoms? • Are clients more or less likely to use condoms? 	
----	---	--

8.	<p>What are FSW perceptions on their negotiation power for protection?</p> <p><u>How easy do you think it is to persuade partners who do not pay you for sex to use a condom?</u></p> <ul style="list-style-type: none"> • Is it always possible to persuade partners who do not pay you for sex to use a condom? • Is this different for main or casual partners? • What issues might people have trying to make partners use condoms? <p>Reminder: Main partner: a husband, boyfriend, or someone you might call an emotional partner that you see regularly whom you do not see as a client and who does not necessarily give you money or gifts in exchange for sex</p> <p>Casual partner: someone you might see from time to time but whom you do not consider to be in a serious relationship with.</p>	
----	--	--

9.	<p>Does disclosure of FSW HIV status affect condom use with romantic/main partners?</p> <p><u>What do you think about disclosing your HIV status to romantic/main partners? Does it affect whether you use a condom?</u></p> <ul style="list-style-type: none"> • Would you disclose your status to a partner? Why? • Have you done it before? What happened? 	
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FGD No.

Date:

Study site:

Name of the facilitator:

Number of participants:

Nick Name: _____

Date of birth (dd/mm/yyyy):

Place of birth: _____

Current place of residence: _____

Highest level of grade completed at school? (Please tick on the line)

☐ No schooling
Grade 10-12

☐ Primary
Higher

☐ Grade 8-10

☐

Marital Status (Please tick on one of the lines)

☐ Single
Widowed

☐ Married

☐ Divorced/Separated

☐

Appendix VIII: Product information sheets



HIV Prevention Product Information Sheet – Choice Information



Oral Pre-Exposure Prophylaxis (PrEP) tablets – Male and Female



- Oral PrEP tablets contain a small amount of HIV prevention medicine
- You **can** use this product without your partner knowing
- Tablets need to be taken more often than other products

What happens if I forget to take a tablet?

Like a contraceptive pill, you can take a tablet up to 24 hours after you missed the dose

How long will side effects last?

Side effects will only occur 1 time in every 60 uses, and last for around 3 hours.

Can I take the tablets whilst I am pregnant?

Yes – the tablets are completely safe to you and your baby

Where could I get these from?

These would be available for free from a pharmacy or clinic, or other places contraceptives are available at the moment. None of these products are currently available as they are still being tested.



SILCS Diaphragm and Microbicide Gel - Female



- The SILCS diaphragm and microbicide gel are put into the vagina before sex, and contain a small amount of HIV prevention medicine
- You **cannot** use these without your partner knowing
- These must be used every time you have sex
- You can wash and re-use the diaphragm using soap and water

What happens if I forget to use the gel and diaphragm when I have sex without a condom?

You will not be protected from HIV or pregnancy

How long will side effects last?

Side effects will only occur 1 time in every 60 uses, and last for around 3 hours.

Can I use the gel and diaphragm whilst I am pregnant?

Yes – both the gel and diaphragm are completely safe to you and your baby

Where could I get these from?

These would be available for free from a pharmacy or clinic, or other places contraceptives are available at the moment. None of these products are currently available as they are still being tested.

How long can I use and re-use the diaphragm for?

As long as you wash the diaphragm with soap and water after every use, you can use the diaphragm for up to 2 years.

Can I sterilise the diaphragm?

Not without damaging the diaphragm. The best way to keep the diaphragm clean is to wash it with soap and water, this method has been shown to be safe and effective.



Microbicide Gel - Female



- Microbicide gel is put into the vagina before sex, and contains a small amount of HIV prevention medicine
- You **cannot** use the gel without your partner knowing
- The gel must be used every time you have sex

What happens if I forget to use the gel when I have sex without a condom?

You will not be protected from HIV or pregnancy

How long will side effects last?

Side effects will only occur 1 time in every 60 uses, and last for around 3 hours.

Can I use the gel whilst I am pregnant?

Yes – the gel is completely safe to you and your baby

Where could I get these from?

The gel would be available for free from a pharmacy or clinic, or other places contraceptives are available at the moment. None of these products are currently available as they are still being tested.

Is the gel applicator single use, or re-usable?

The applicator is single use i.e. you use it once then throw it away. You would be given many applicators to fill from a single tube of gel.



The Vaginal Ring - Female



- The vaginal ring is put inside the vagina, and contains a small amount of HIV prevention medicine
- You **can** use this without your partner knowing
- The ring needs to be used less often than other products because it stays in the vagina for longer periods of time

What happens if I forget to get a new ring?

You will not be protected from HIV or pregnancy

How long will side effects last?

Side effects will only occur 1 time in every 60 uses, and last for around 3 hours.

Can I use the ring whilst I am pregnant?

Yes – the gel is completely safe to you and your baby

Where could I get these from?

You would be able to get the ring fitted for free from staff at a pharmacy or clinic, or other places contraceptives are available at the moment. None of these products are currently available as they are still being tested.



The Injection – Male & Female



- The injection is the same as any other injections you have had, but it contains a small amount of HIV prevention medicine
- You **can** use this without your partner knowing
- The injection needs to be used less often than some other products

What happens if I forget to get a new injection?

You will not be protected from HIV or pregnancy

How long will side effects last?

Side effects will only occur 1 time in every 60 uses, and last for around 3 hours.

Can I get the injection whilst I am pregnant?

Yes – the gel is completely safe to you and your baby

Where could I get these from?

You would be able to receive an injection from staff at a pharmacy or clinic, or other places contraceptives are available at the moment. None of these products are currently available as they are still being tested.

Appendix IX: Preferences for ARV based HIV prevention methods among adult men and women, adolescent girls and female sex workers in Gauteng Province, South Africa: A protocol for a discrete choice experiment

Overview of paper

The products DCE was developed by using qualitative work led by the supervisor of this thesis in 2005[1], brief literature reviews (led by a colleague before I joined the project), and extensive piloting and pretesting. A 3-round, iterative set of pre-pilot interviews assessed respondent understand of the choice tasks, and informed minor changes before a larger pilot refined outstanding issues before final implementation.

The gold standard in DCE development involves an inductive qualitative process where attributes and levels are identified through qualitative interviews and/or focus group discussions[2]. I was unable to carry out primary qualitative data collection for this DCE due to budget and time constraints due to the end-date of a grant, however, to account for this the DCE outline and design was presented multiple times to a range of HIV and DCE experts in the UK and South Africa, and weight given to participant comments in piloting, however it is a limitation of this study that primary qualitative work was not conducted.

Reference list

1. MacPhail, C., et al., *Managing men: women's dilemmas about overt and covert use of barrier methods for HIV prevention*. Culture, Health & Sexuality, 2009. **11**(5): p. 485-497.
2. Hensher, D., J. Rose, and W. Greene, *Applied Choice Analysis: Second Edition*. 2015, Cambridge: Cambridge University Press.



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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Matthew Quaife
Principal Supervisor	Fern Terris-Prestholt
Thesis Title	Using stated preferences to estimate the impact of new HIV prevention products in South Africa

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	BMS Open		
When was the work published?	2017		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	no - open access	Was the work subject to academic peer review?	

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Conceptualised, wrote first draft + finalised w/ co-author comments.
--	--

Student Signature: _____

Date: 17/7/17

Supervisor Signature: _____

Date: 17/7/17

BMJ Open Preferences for ARV-based HIV prevention methods among men and women, adolescent girls and female sex workers in Gauteng Province, South Africa: a protocol for a discrete choice experiment

Matthew Quaife,^{1,2} Robyn Eakle,^{1,2} Maria Cabrera,² Peter Vickerman,^{1,3} Mottalepule Tsepe,⁴ Fiona Cianci,⁵ Sinead Delany-Moretlwe,² Fern Terris-Prestholt¹

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ABSTRACT

Introduction: For the past few decades, condoms have been the main method of HIV prevention. Recent advances in antiretroviral (ARV)-based prevention products have substantially changed the prevention landscape, yet little is known about how popular these products will be among potential users, or whether new methods might be used in conjunction with, or instead of, condoms. This study will use a discrete choice experiment (DCE) to (1) explore potential users' preferences regarding HIV prevention products, (2) quantify the importance of product attributes and (3) predict the uptake of products to inform estimates of their potential impact on the HIV epidemic in South Africa. We consider preferences for oral pre-exposure prophylaxis; a vaginal microbicide gel; a long-acting vaginal ring; a SILCS diaphragm used in concert with gel; and a long-acting ARV-based injectable.

Methods and analysis: This study will gather data from 4 populations: 200 women, 200 men, 200 adolescent girls (aged 16–17 years) and 200 female sex workers. The DCE attributes and design will be developed through a literature review, supplemented by a thematic analysis of qualitative focus group discussions. Extensive piloting will be carried out in each population through semistructured interviews. The final survey will be conducted using computer tablets via a household sample (for women, men and adolescents) and respondent-driven sampling (for female sex workers), and DCE data analysed using a range of multinomial logit models.

Ethics and dissemination: This study has been approved by the University of the Witwatersrand Human Research Ethics Committee and the Research Ethics Committee at the London School of Hygiene and Tropical Medicine. Findings will be presented to international conferences and peer-reviewed journals. Meetings will be held with opinion leaders in South Africa, while results will be disseminated to participants in Ekurhuleni through a public meeting or newsletter.

Strengths and limitations of this study

- This study uses a novel discrete choice experiment (DCE) to elicit people's preferences for new antiretroviral (ARV)-based HIV prevention products.
- The results of the DCE will allow us to explore how respondents value different product characteristics. We will also be able to predict whether products will be used alongside, or instead of condoms, a critical element of assessing their potential impact.
- We will draw out policy recommendations from our findings, in particular informing mathematical models to evaluate the impact and cost-effectiveness of a range of new prevention products.
- The DCE choice tasks are hypothetical in nature and will be carried out in Ekurhuleni Metropolitan Municipality, near Johannesburg, South Africa. The results may not be generalisable to other settings. Female sex workers will be recruited through respondent-driven sampling, rather than a randomised method.

INTRODUCTION

Despite intense efforts to reduce HIV incidence, its estimated prevalence remains high in South Africa. The fourth national population-based survey conducted by the Human Sciences Research Council, estimated prevalence to be 12.6% in 2012, an increase on the previous survey estimate of 10.9% in 2008.¹ This increase may be explained partly by expanded access to antiretroviral (ARV) treatments and associated reductions in mortality, however, there is also evidence of continued sexual transmission of HIV in those aged 15 years or older. HIV

infection is not borne equally in the South African population; women are 1.4 times more likely to be living with HIV compared to men, while adolescent girls (aged 15–19 years) are at 8 times greater risk of being HIV positive than boys of the same age.¹ Female sex workers (FSWs) are designated a key population for HIV treatment and prevention activities, and are around four times more likely to be living with HIV than South African women of reproductive age from the general population.^{2 3}

The HIV prevention landscape continues to shift substantially, not least due to emerging evidence that ARV drugs can be used for HIV prevention. The HPTN 052 trial demonstrated the ability of ARVs to reduce the infectiousness of HIV positive persons through suppressing viral loads, and led to the development of treatment-as-prevention programming.⁴ Furthermore, ARV-based oral pre-exposure prophylaxis (PrEP) has been shown to offer a high degree of protection from HIV acquisition in different populations and contexts worldwide.^{5–9} In 2012, WHO recommended oral PrEP for use in specific 'high-risk' populations, such as sero-discordant couples. This recommendation was broadened in September 2015 with PrEP recommended for any person at 'substantial risk' of HIV acquisition, and not necessarily restricted to those in key populations.¹⁰

Despite the success and subsequent licensure of oral PrEP, there is an increasing recognition that the characteristics of effective prevention options may vary across different population groups. It is important that prevention options are tailored to fit well with the lifestyles of potential users, and recent efforts have focused on developing novel methods of delivering ARV drugs for HIV prevention. Outside of oral PrEP, there are numerous products in various stages of development including: vaginal microbicide gels used daily or at every sex act; long-acting vaginal rings; a SILCS diaphragm used in concert with gel; and long-acting injectable products.^{5 6 8 11–13}

Problems with adherence have plagued clinical trials of shorter-acting products such as microbicide gels, highlighting the need for methods that are attractive and easy for people to use.^{6 9} The development of longer acting products, such as the monthly applied vaginal ring or the three-monthly injection, has the potential to increase adherence, uptake and thus effective coverage.^{14 15} However, until products have been developed and rolled out to a population, it is difficult to accurately predict whether or how much they will be used, or whether they will be used in addition to, or instead of condoms which offer multipurpose protection.¹⁶

Attention has also turned to the potential for new products to meet the broader reproductive and sexual health needs of many individuals. These needs are not limited to protection against HIV and other sexually transmitted infections (STIs), but also access to safe and reliable contraceptives. Currently, the only products which protect against HIV, STIs and unwanted

pregnancies are the male and female condoms, and so there may be demand for additional product choices which confer combination protection. As such, considerable research has focused on developing multipurpose technologies (MPTs) which offer protection against HIV, STIs and pregnancy.¹⁷ Efficacy trials for MPTs are planned and products could be made available on the market in the next decade.^{11 14}

In the context of these advances in the field of HIV prevention, it is important to identify and explore the determinants of demand for new technologies. Understanding user preferences can not only assist prevention efforts by predicting product uptake, but also help refine the development of new products. We plan to undertake a study that will use a discrete choice experiment (DCE) to quantify potential users' stated preferences of ARV-based prevention products in a South African setting, predict uptake of new products, and assess the extent to which condom use might be reduced following their introduction.

DCEs are, theoretically, robust economic tools, and can be particularly informative when there are little or no data on observed behaviour.^{18–20} DCEs ask people to choose between a number of hypothetical scenarios, where each choice is described by a set of attributes. By assessing how choices vary according to different attribute levels, researchers are able to assess what is important to people as they choose. Furthermore, DCEs allow researchers to quantitatively elicit the key drivers of individuals' decisions, and can predict future behaviour.²¹ DCE methods have been used extensively in fields of applied economics, particularly transport and environmental economics.^{22–24} In health, they have been applied across a range of disease prevention areas including voluntary medical male circumcision, vaccination, STI treatment and contraception.^{25–28}

A particularly novel use of this research will be for subsequent work to integrate DCE-derived uptake predictions from this study within an infectious disease-modelling framework to estimate the potential impact and cost-effectiveness of introducing new HIV prevention products. Such models often rely on assumed levels of uptake based on expert opinion, or uptake of similar interventions.²⁹ These assumptions are frequently not based on data, and so are likely to produce inaccurate projections. This study will build on previous research suggesting that DCEs may provide more data-driven, dynamic and realistic estimates of product uptake in the absence of observed data.³⁰

METHODS AND ANALYSIS

Overview of approach and methods

This study will build on previous mixed-methods research to explore consumer preferences for HIV prevention products in South Africa. Primary formative research will be carried out among target groups before the implementation of a survey with 800 participants: 200 men and 200

women aged between 18 and 45 years, randomly sampled from the general population, 200 adolescent girls (aged between 16 and 17 years), also randomly sampled from the general population, and 200 FSWs sampled using respondent-driven sampling, a common approach for collecting data from hard-to-reach populations.³¹

The DCE will be carried out among all self-reported HIV-negative persons sampled. Although self-reported HIV status is not necessarily a reliable indicator of serostatus, it can still be useful for hypothetical DCE surveys, assuming that respondents answer according to their perceived HIV status. In an effort to maximise reporting accuracy, we will use an experienced team of interviewers with additional training, focusing on making participants comfortable, and reinforcing confidentiality throughout the interview.

A 2005 study in the same municipality used qualitative focus group discussions (FGDs) and individual interviews to develop a DCE on a set of HIV prevention products under development at the time.²⁹ The research identified which product characteristics (or attributes) consumers valued, how the levels of these might vary, and optimal ways to present these to participants in a choice experiment. To develop relevant and meaningful choice tasks, the current study will build on this previous formative research, alongside an updated review of the literature, and intensive piloting with each population.









In a DCE, respondents are presented with a number of options which are each described by attributes of particular levels. Respondents are first asked to choose their most favoured option from two or more alternatives, and then they continue with this process which is repeated over a number of different choice sets. Attribute levels are systematically varied between sets according to an experimental design which aims to maximise the statistical efficiency of data collection. For each choice set, it

is assumed that respondents choose the scenario which would give them the most benefit, and choices are, therefore, indicative of an underlying utility function. Econometric analysis of DCE data estimates the utility functions of respondents which quantitatively weights the value placed on each attribute. A more detailed analysis is possible through the inclusion of sociodemographic or other information as explanatory variables in these functions.³²

DCEs give a quantitative indication of the strength of an individual's preference for one attribute (such as efficacy in preventing HIV infection) relative to another (such as frequency of application). Results from DCEs are conducive to directly informing policy by allowing inference of the key drivers of individual behaviour in responding to different policy environments, and enable the simulation of how choices might change under different circumstances. An example of a DCE is shown in figure 1, where figure 1A represents a vaginal ring, and figure 1B and 1C different injectable products. The opt-out alternative in the final column will be presented as what a respondent reported using in their last sexual encounter, that is, the attributes of a condom if the participant used a condom, or the characteristics of using no protection otherwise. This is to allow the estimation of unconditional demand for new products.

The study design is shown in figure 2, and consists of three stages: an extensive formative phase (including generating an initial design, piloting and pretesting of the DCE), implementation of the DCE and data analysis and publication. The DCE design began in July 2015 and piloting in September 2015. Data collection for the final DCE is expected to be carried out between October and December 2015. This study will conform to the best-practice guidelines of the International Society for Pharmacoeconomics and Outcomes Research

Here are the products and this is what they do. Please select the product you would most prefer.

	1	A	B	C		
Product						
HIV protection		95% risk reduction 19 of 20 people remain HIV negative	55% risk reduction 11 of 20 people remain HIV negative	95% risk reduction 19 of 20 people remain HIV negative		95% risk reduction 19 of 20 people remain HIV negative
Pregnancy prevention		Does not prevent pregnancy	Prevents pregnancy	Does not prevent pregnancy		Prevents pregnancy
Frequency of use		Use once per month	Use two times per year	Use four times per year		Every sex
Protection against other infections		STI Protection Does not prevent STIs	STI Protection Does not prevent STIs	STI Protection Prevents STIs		STI Protection Prevents STIs
Side effects						

OR



	Nothing	Condom
HIV protection	0% risk reduction 0 of 20 people remain HIV negative	95% risk reduction 19 of 20 people remain HIV negative
Pregnancy prevention	Does not prevent pregnancy	Prevents pregnancy
Frequency of use	Never	Every sex
Protection against other infections	STI Protection Does not prevent STIs	STI Protection Prevents STIs
Side effects		

Figure 1 Example of a discrete choice experiment choice task to elicit HIV prevention product preferences from HIV negative women.

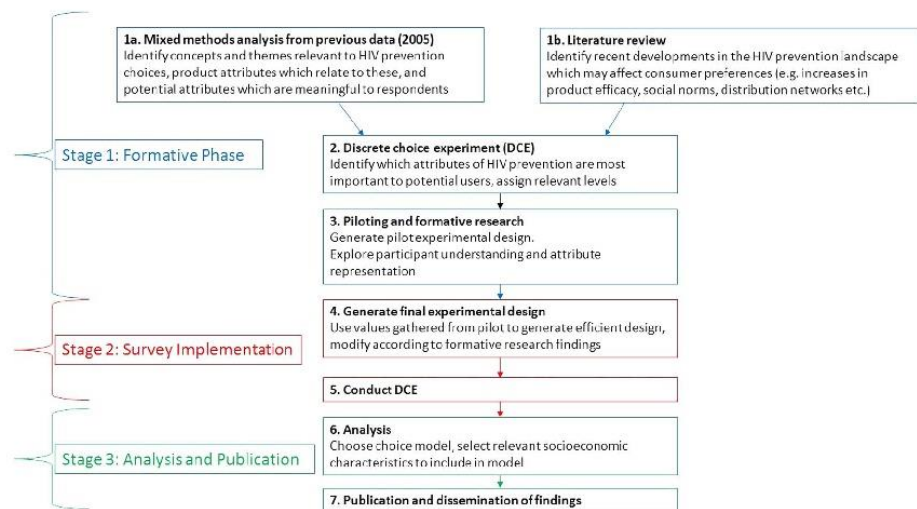


Figure 2 Study design. DCE, discrete choice experiment.

Guidelines for Good Research Practices for conjoint analysis in health.³³

Stage 1: formative phase—development and piloting of choice tasks, attributes and levels

A thematic analysis of qualitative data gathered in an earlier study²⁹ led to the identification of key attributes which were important to the respondents' choice of a HIV prevention product. These will be explored in the context of more recent literature to account for evolution in the HIV prevention field, for example, changes in technology (eg, product efficacy) and policy (eg, potential for free provision by the South African Government). Then, between 5 and 10 'pre-pilot' interviews will be carried out in each population to assess participants' understanding of background questions and DCE choice tasks, explore the most meaningful

representations of attributes and levels, and identify any issues with the tablet-based implementation of the DCE. The pre-pilot stage will be critical in creating clear, relevant and realistic choice sets which are presented to participants in an understandable manner. The DCE to be piloted is unlabelled, meaning all products will not be presented at once, but each will appear as an available alternative according to the experimental design. The six attributes of the DCE and their levels are shown in table 1.

We will include five new prevention products, chosen to reflect the range of potential ARV delivery mechanisms. Some (eg, oral PrEP) are fully developed and are in the later stages of global licensing, while others (eg, injectables) are a few years from efficacy trials and potential roll-out. Women will be presented with the full range of products, while men will only be presented

Table 1 Attributes and levels

Attribute	Levels
Product	Oral pre-exposure prophylaxis, microbicide gel, microbicide gel with SILCS diaphragm, vaginal ring, injectable pre-exposure prophylaxis
HIV protection	55%, 75%, 95%
Pregnancy prevention	Prevents pregnancy, does not prevent pregnancy
Frequency of use*	Every time you have sex, once per day, once per week, once per month, once per 3 months, once per 6 months, once per year
Protection against other STIs	Protects against other STIs, does not protect against other STIs
Side effects (probability of occurrence fixed)	Stomach cramps/pain, nausea/feeling sick, dizziness, none

*As no product can be used at all frequencies, the design will contain constraint terms where only relevant frequencies will be presented alongside products. Frequencies were chosen to be informative for product development: oral PrEP—daily, weekly, monthly; microbicide gel—coitally; SILCS diaphragm and microbicide gel—coitally, daily; vaginal ring—weekly, monthly, three-monthly, six-monthly; injection—three-monthly, six-monthly, annually. SILCS; STI, sexually transmitted infections.

with male-initiated options (ie, oral PrEP and injectables). We include two products based on microbicide gels, despite recent unsuccessful effectiveness trials.⁶⁻⁹ Trial results suggest that gels were efficacious when used adherently, however, many participants were not able to use the products consistently enough as part of everyday life. Including these products in the DCE will allow us to explore how preferences for products vary by characteristics, such as frequency of use and potential side effects, and provide an opportunity to compare DCE predictions to reality. We note that common side effects were chosen through reports from PrEP trials and ART regimens using ARV drugs.³⁴⁻³⁵

FGDs will be carried out with FSWs, as the risk factors and sexual relationships of this group are likely to be substantively different from other population, while it was noted that there was a gap in the literature and in local knowledge on FSW preferences. It is a limitation of this study that we are unable to carry out FGDs with men or adolescent women; however, we will use the expertise and experience of local collaborators alongside identifying substantive literature to assess relevant attributes for these groups. In the FSW FGD, themes related to HIV prevention choices and negotiation of protection with clients and partners will be explored in four FGDs with between 8 and 12 participants in each. The qualitative data from the focus groups will then be analysed using thematic analysis to inform the final version of the DCE survey tools.³⁶ These discussions will provide novel insights into decision-making by FSWs around HIV prevention which have never been explored in a DCE context before.

The DCE will be piloted through an initial fractional factorial design which will be generated by specialist NGENE software³⁷ and tested face to face with a subsample of 20 respondents, five from each population group (men, women, adolescent girls and FSWs). These pilots will aim to assess how well respondents understand questions and responses, whether tablet-based enumeration is feasible and reliable, and explore different presentations of DCE tasks and attributes. Furthermore, the responses from these DCE tasks will be analysed using a multinomial logit model (MNL) to obtain point estimates of utility function parameters. These estimates will be used in generating a statistically efficient design for the final DCE.

The attributes and levels shown above yield 1260 possible product profiles, far too great a number to present to all participants. Recent advances in DCE design have led to the development of 'efficient' designs which, when informed by prior information from a pilot study and/or the literature, offer more reliable parameter estimates when compared with traditional orthogonal designs. To ensure realistic choice data and avoid overestimating demand for new products,³² participants can opt out of choosing a new product with a fourth alternative presented of 'do what I did last time' (ie, use a condom or nothing). Since an unlabelled design is used

to reduce the number of choices within a set from six to four, it is likely (and certain in the male DCE) that some products will be presented twice in the same choice set, with different attribute levels. Interviewers will be fully trained to explain this nuance to participants.

Finally, data will be captured in the final questionnaire on salient background characteristics of participants including: age, gender, quality of life, reproductive history, relationship history and HIV knowledge. This data will allow the analysis of how preferences are shaped by life circumstances, for example, if a respondent is seeking to conceive with a partner. Through framing choice tasks around the last sex act, we will be able to explore how preferences may vary by partner type, for example, between non-commercial and commercial partners of FSWs, or between long-term and short-term sexual relationships. Data will also be gathered on the gender of respondents' most recent sexual partner. The piloting process will inform which characteristics should be included in final data analysis as explanatory variables for preferences in HIV prevention products. Finally, we note that while trials of some products (oral PrEP and a vaginal ring) will be ongoing in some populations in South Africa during this study,³⁸ the geographically concentrated and research-naïve populations chosen for this work are very unlikely to have experience of using these (eg, through participation in trials). We will record if participants have prior experience of using any of these products.

Stage 2: administration of DCE

Participants and recruitment

The survey and DCE will be administered using Open Data Kit (<https://opendatakit.org/>) software on tablet computers. The acceptability and feasibility of tablet-based data collection will be assessed during the formative stage, although it is expected that it will minimise missing data, and reduce laborious data entry and cleaning.³⁹⁻⁴⁰ Participants will be given a ZAR 50 (GBP £2.50) voucher as compensation for their time. Participants will be asked to self-report their HIV status, and we aim to maximise accuracy in reporting through careful confidentiality and sensitivity training of the interviewer team, which has considerable experience in collection of HIV and sexual health data.

To ensure that choices are relevant and meaningful to participants, three steps will be taken to maximise the realism of choice scenarios. First, all interviewers will be equipped with a full set of example products: a real SILCS diaphragm, alongside placebo PrEP tablets (similarly coloured, shaped and sized), vaginal rings, microbicide gels and injections (an empty syringe). Participants will be encouraged to touch and explore the products as much as they wish before beginning choice tasks. Second, interviewers will be thoroughly trained and tested on how to describe products to participants. In addition, concise and clear information sheets will be used when explaining the tasks, products and attributes.

Third, the statistical design of the DCE will be such that only relevant products are presented to different groups, and relevant attributes for different products. For example, only injectable and PrEP options will be presented to men, while the frequency of injections will be restricted to between once per month and once per year.

If participants choose an ARV-based, non-condom product, they will subsequently be asked whether or not, if the product was available, they would have used it the last time they had sex. If they indicate that they would, they will be asked whether they would have used it alongside, or instead of, a condom. This will enable us to ascertain whether new products will be used in combination with, or in substitute of, condoms. Since there is likely to be no additional benefit from dual use of ARV-based products, nor would medical advice suggest this would be something users should do, the DCE framework does not allow for the combination use of ARV-based products, except the SILCS diaphragm which is used in concert with gel.

Primary data will be collected in Ekurhuleni Metropolitan Municipality, Gauteng Province. The Municipality was selected as the study site because it contains a broad range of residential contexts, representing a range of demographic, socioeconomic and cultural characteristics. We employ a proportional cluster sampling strategy, stratified by population. For the 200 men and 200 women, the nature of the household sampling method means that we may be able to interview both cohabiting partners in a relationship; assuming a sufficient number of individuals in cohabiting relationships are available and consent to participate, analysis of preferences within relationships would be a particularly novel element of this research.

Different enumeration teams will interview respondents from each group. For the general population, a specialist local data collection firm with over 20 years of experience, Progressus Research and Development (<http://www.progressus.co.za/>), will manage the survey process, generate the sampling design, and carry out the DCE. On finding an adult present in a household, the interviewer will identify him/herself, explain the study, and request permission to note down all women, men and adolescent girls living in the house ordered by age. We expect the whole survey, including DCE, will take around 30–45 min to complete.

Two hundred FSWs will be recruited through RDS. We will employ peer educators who will first locate sex work 'hotspots' in the Vosloorus area, before selecting 7–10 seeds among FSWs operating in different areas such that different social networks are reached (eg, FSWs working in brothels, on the street or in bars or taverns). These women will be invited to participate in the study and given a ZAR 50 (GBP £2.50) voucher as compensation for their time, before receiving three coupons containing the study information to distribute to colleagues. When one of these colleagues attend the study site, both

they and their recruiter receive a small incentive in the form of a ZAR 20 (GBP £1) voucher. The amount of compensation was based on similar studies among FSWs in South Africa, and is designed to be high enough to compensate for potential loss of one client during study participation, but not so high as to encourage significant fraudulent enrolment.

Sample size

The DCE literature has not yet reached consensus on the best way to successfully estimate the sample size required in a DCE study to return meaningful, statistically robust parameter estimates. Applying the popular rule of thumb of Johnson and Orme,^{41–43} we estimate that a sample size of 90 should be sufficient to estimate parameters of the DCE structure shown in figure 1. Similarly, the literature suggests that between 20 and 30 observations per choice set can provide precise parameter estimates.^{18 44} This indicates that our sample size of 800 will be sufficient to estimate parameters over the entire population, as well as to explore any variations in preferences which might exist between groups.

Stage 3: data analysis

Results from this study will aid future development and rollout of HIV prevention products by identifying key product attributes likely to influence an individual's decision to use such products. Although there are a number of ways to analyse DCE data, the literature generally advises to start with a simple MNL model, and progressively explore other model specifications.³² A notable restriction of the MNL model is that it assumes the 'irrelevance of independent alternatives' (IIA), specifically that the odds of choosing one class over another does not depend on the wider set of alternatives. This is often not realistic, and we will employ discrete choice models such as the mixed MNL (MMNL) and generalised MNL (GMNL) models. These relax some assumptions of the MNL model (including the IIA restriction) as model coefficients are allowed to vary over individuals through the inclusion of stochastic components. Choice data from this study will be analysed through MNL, MMNL, nested logit and generalised MMNL models to fully explore heterogeneity in the data.³²

Interactions between DCE attributes and respondent characteristics (such as the interaction between perceived HIV risk and preferences for product efficacy) will be explored by their inclusion as explanatory variables when estimating utility functions. Model results will be presented as parameter estimates with SEs. The marginal rate of substitution between attributes will also be calculated.

Finally, the RDS sample among FSWs will be analysed with consideration of the non-random, chain-referral nature of the data through mathematical weighting to compensate for non-random participant recruitment. RDS data require a number of assumptions to hold for statistical inferences to be valid; however, when

attempting to reach hidden populations such as FSWs, RDS is an increasingly popular and reasonably robust method.^{31 45}

ETHICS AND DISSEMINATION

Ethical considerations

This study has been reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee and the Research Ethics Committee at the London School of Hygiene and Tropical Medicine. All participation in the DCE, alongside supporting qualitative studies will be voluntary and subject to completion of written informed consent. When interviewing adults in households where adolescent girls aged 16–17 years are present, interviewers will ask for assent from the young woman, aim to obtain guardian consent, and interview the adolescent. The informed consent processes will be administered in private (including from a parent or guardian of an adolescent subject). A comprehensive distress protocol will ensure that participants who reveal distressing or harmful events during the survey will be referred to named persons at local clinics and NGOs.

All information provided by respondents will be kept secure and confidential. Paper-based informed consent forms and household survey frames will be kept separately from questionnaire data to protect the identity of the participants. Participants do not need to use their real names in any of the interview formats, while the background survey will not collect any identifiable information from respondents outside of salient socio-economic and sexual history characteristics. It will be made clear to all participants that they have the right to withdraw from the research at any point in time. Participants will be informed that there is no immediate benefit to them for taking part in the study, but that the information they give can help develop future products and services. Participants will receive a ZAR 50 (£2.50) voucher as a token of appreciation for their time.

DISSEMINATION

Results will be published through peer-reviewed journals and via national and international conference presentations. Meetings will be held with opinion leaders in South Africa and organisations working in the area of HIV prevention. Results will be disseminated to participants in Ekurhuleni through a public meeting or newsletter; extra care will be taken here to ensure participant anonymity.

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Appendix X: FGD Poster as presented at HIV R4P 2016



Sex work, risk and incentives: an exploration of risk perceptions and relationship dynamics among female sex workers in Ekurhuleni, South Africa

Authors: Robyn Eakle, Matthew Quaife, Maria Cabrera, Peter Vickerman, Sinead Delany-Moretlwe, Fern Terris-Prestholt

INTRODUCTION

Female sex workers (FSWs) are a focal point for concerted HIV prevention, treatment and wider health programming with the launch of South Africa's National Plan for Sex Workers. As a population with high HIV prevalence, maintaining a negative HIV status is imperative and new HIV prevention options could aid in this effort.

METHODS

Four FGDs were held among FSWs (n=48) in Ekurhuleni to aid in the design and analysis of a discrete choice experiment (DCE). We used snowball sampling to recruit participants through peer educator networks. FGDs explored:

- relationship dynamics among clients and other sexual partners,
- disclosure of HIV status,
- how offers of monetary gain shape perceptions of clients and change the likelihood of selling unprotected sex,
- other elements pertaining to the DCE.



RESULTS

Women expressed in-depth knowledge of HIV transmission, prevention and treatment. They were keenly aware of occupational risks relating to health, economic stability, and violence. Most women were reticent to risk their lives for money, but some admitted that when money was scarce, risks might be taken with clients to be able to pay rent and buy food. However, trust in clients, or lack thereof, was a universal and cross-cutting theme which translated more often into strict condom use with clients, acute perception of power dynamics, and expert negotiation skills around price and protection. Disclosure of HIV status was limited to main partners, with workplace disclosure thought to impact potential monetary earnings. Results were used to inform the design and analysis of two discrete choice experiments carried out in late 2015.

CONCLUSIONS

Women in this population of FSWs were generally knowledgeable and empowered to protect themselves, but acknowledged the potential for risk taking when under social or financial pressure. HIV prevention research and programming must take into account the nuanced reality of women's lives and offer a range of options, with future product development focusing on combined protection methods.

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